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INQUIRY INVESTIGATION OF ENVIRONMENTAL POLLUTION AND DAMAGE DUE TO VEHICULAR TRAFFIC IN URBAN AREAS

NOISE AND POLLUTANTS

ENVIRONMENTAL PROTECTION AGENCY

1974

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INQUIRY
INVESTIGATION OF ENVIRONMENTAL POLLUTION AND DAMAGE DUE TO VEHICULAR TRAFFIC IN URBAN AREAS
- NOISE AND POLLUTANTS -

[EG-Enquête
Untersuchung der Umweltbelästigung und Umweltschädigung
durch den Strassenverkehr in Stadtgebieten
- Lärm und Abgase -]

H. W. Schlipköter

Association of German Engineers,
AGE Commission for Noise Abatement,
AGE Commission for Purification of
the Atmosphere, under the direction
of the Federal Ministry for Traffic,
203 pp., Düsseldorf, 1974.

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Düsseldorf, October 4, 1972
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INQUIRY

INVESTIGATION OF ENVIRONMENTAL POLLUTION AND DAMAGE DUE TO VEHICULAR TRAFFIC IN URBAN AREAS — NOISE AND POLLUTANTS —

Partial Study II. 2

Investigation of the Psychological and Physiological Effects of Automobile Exhaust Gases on the Urban Population

Prepared in association with:

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1. Proposal

The present report on

"Investigations on the Physiological and Psychological Effect of Automobile Exhaust Gases on the Population"

is a partial study for a research project assigned by the Association of German Engineers, operating under instructions of the Federal Traffic Ministry, under the heading:

"Investigations on Environmental Pollution and Damage Due to Vehicular Traffic in Urban Areas (Noise and Exhaust Gases)".

The objective of this report is to evaluate presently available information in order to:

1. determine the relationships between exhaust gas pollution from motor vehicles and the resulting damage to the health of, as well as the stress on, the population in urban areas, and

2. ascertain the possible empirically based parameters of the human capacity for environmental stress.

The results of this report are to be utilized in establishing the costs of environmental pollution by vehicular traffic in urban areas.

2. General Background

The atmosphere contains increasing amounts of noxious materials which, particularly in densely populated areas, lead to rapidly rising air pollution due to the accumulation of various aerial pollutants. Since in these areas (due to high-rise building), we also have to deal with reduced air circulation, the pollutants which are emitted remain for extended periods of time in the layers of the atmosphere close to the ground, thereby impairing the physical and psychological effectiveness and interfering with the well-being of the population.

In addition to domestic heating and the presence of industrial and business facilities, it is the motor vehicles which significantly contribute to air pollution in congested areas. The increase in vehicle traffic in the Federal Republic can be seen from the tripling of registered motor vehicles within the last 10 years. We must consider, moreover, that at least 30 - 40% of the pollutants due to vehicular traffic impinge on the congested areas in which 33% of the present total population of the Federal Republic spend their lives. While the average population density of the BDR (Federal Republic of Germany) equals 245 inhabitants/km^2, it increases in congested areas by a factor of 13, to 3220 inhabitants/km^2.

If the present trend continues — i.e., further increase in vehicular traffic and population density due to the blending of industrial and residential areas — we must expect constantly increasing detrimental effects of automobile exhaust gases on large sectors of the population. Even today, it is assumed that vehicular traffic contributes 50% (1,000,000 t/yr) of the air pollution in urban areas. An isolated value of that order, to be sure, is very inaccurate and expresses little about the contribution of motor vehicles to air pollution, or about the relative danger of individual pollutants in exhaust gases to the human organism. In investigating such effects, therefore, it is necessary to proceed from isolated pollutants to groups of pollutants and so to pin-point the poisonous or potentially poisonous materials, the removal of which is today of prime importance for the protection of the people's health.

3. Form and Content of the Term "Air Pollution by Automobile Exhaust Gases"

3.1. Automobile Exhaust Gases

The term automobile exhaust gases defines a mixture emitted in large quantities by internal combustion engines (primarily private cars or vans) as well as, to a lesser degree, by Diesel engines (primarily trucks and buses). It contains an extraordinarily large variety of known and unknown organic compounds, whose number greatly surpasses that of the inorganic components.

By way of demonstrating the extraordinary complexity of the concept automobile exhaust gases, we offer a list — by no means complete — of the 164 organic and inorganic components which have been isolated so far:

I. Inorganic pollutants

1. Carbon monoxide (CO)
2. Nitrous oxide (NO)
3. Nitrogen dioxide (N_2O)
4. Nitric oxide (NO_2)
5. Lead compounds (lead oxides, lead halides)
6. Soot (carbon)

II. Organic pollutants

Paraffins:

1. Methane (CH_4)
2. Ethane (C_2H_6)
3. Propane (C_3H_8)
4. n-Butane (C_4H_{10})
5. i-Butane (C_4H_{10})
6. n-Pentane (C_5H_{12})

(list continued on following page)

7. i-Pentane (C_5H_{12})
8. n-Hexane (C_6H_{14})
9. 2,2-Dimethylbutane (C_6H_{14})
10. 2,3-Dimethylbutane (C_6H_{14})
11. 2-Methylpentane (C_6H_{14})
12. 3-Methylpentane (C_6H_{14})
13. n-Heptane (C_7H_{16})
14. 2,2,3-Trimethylbutane (C_7H_{16})
15. 2,2-Dimethylpentane (C_7H_{16})
16. 2,3-Dimethylpentane (C_7H_{16})
17. 2,4-Dimethylpentane (C_7H_{16})
18. 3,3-Dimethylpentane (C_7H_{16})
19. 2-Ethylpentane (C_7H_{16})
20. 2-Methylhexane (C_7H_{16})
21. 3-Methylhexane (C_7H_{16})
22. n-Octane (C_8H_{18})
23. 2,2,3-Trimethylpentane (C_8H_{18})
24. 2,2,4-Trimethylpentane (C_8H_{18})
25. 2,3,4-Trimethylpentane (C_8H_{18})
26. 2,2-Dimethylhexane (C_8H_{18})
27. 2,3-Dimethylhexane (C_8H_{18})
28. 2-Methylheptane (C_8H_{18})
29. 3-Methylheptane (C_8H_{18})
30. 4-Methylheptane (C_8H_{18})
31. n-Nonenes (C_9H_{20})
32. 2,2,5-Trimethylhexane (C_9H_{20})

Napthenes:

1. Cyclopentane (C_5H_{10})
2. Methylcyclopentane (C_6H_{12})
3. Cyclohexane (C_6H_{12})
4. Methylcyclohexane (C_7H_{14})
5. Ethylcyclohexane (C_8H_{16})
6. Cyclohexene (C_6H_{10})
7. 1-Methylcyclohexene (C_7H_{12})

Olefins:

1. Ethylene (C_2H_4)
2. Propylene (C_3H_6)
3. 1,3-Butadiene (C_4H_6)
4. Butene-(1) (C_4H_8)
5. Butene-(2) (C_4H_8)
6. i-Butene (C_4H_8)
7. 2-Methyl-1,3-butadiene (C_5H_8)
8. 1,3-Pentadiene (C_5H_8)
9. Pentene-(1) (C_5H_{10})
10. Pentene-(2) (C_5H_{10})
11. Methyl-butene-(1) (C_5H_{10})
12. 2-Methyl-butene-(2) (C_5H_{10})
13. 2-Methyl-butene-(3) (C_5H_{10})
14. Hexene-(1) (C_6H_{12})

(List continued on following page)

15. Hexene-(2) (C_6H_{12})

16. Hexene-(3) (C_6H_{12})

17. 2-Methyl-pentene-(1) (C_6H_{12})

18. 2-Methylpentene-(2) (C_6H_{12})

19. 3-Methylpentene-(2) (C_6H_{12})

20. 2-Methyl-pentene-(3) (C_6H_{12})

21. 3-Methyl-Pentene-(2) (C_6H_{12})

22. 2-Methyl-pentene-(3) (C_6H_{12})

23. 2-Methyl-pentene-(4) (C_6H_{12})

24. 2-Ethyl-butene-(1) (C_6H_{12})

25. 2,3-Dimethyl-butene-(1) (C_6H_{12})

26. 2,3-Dimethyl-butene-(2) (C_6H_{12})

27. Heptene-(1) (C_7H_{14})

28. Heptene-(3) (C_7H_{14})

29. 2-Methyl-hexene-(4) (C_7H_{14})

30. 2-Methyl-hexene-(5) (C_7H_{14})

31. 3,4-Dimethyl-pentene-(1) (C_7H_{14})

32. 3,4-Dimethyl-pentene-(2) (C_7H_{14})

33. 2,3,3-Trimethyl-butene-(1) (C_7H_{14})

34. Octene-(1) (C_8H_{16})

35. Octene-(2) (C_8H_{16})

36. 2-Ethyl-hexene-(1) (C_8H_{16})

37. 2-3-Dimethyl-hexene-(2) (C_8H_{16})

38. 2,4,4-Trimethyl-pentene-(1) (C_8H_{16})

39. 2,4,4-Trimethyl-pentene-(2) (C_8H_{16})

40. 2,6-Dimethyl-heptene-(3) (C_9H_{18})

Alkines:

1. Acetylene (C_2H_2)

2. Propyne (C_3H_4)

3. Propadine (C_3H_4)

Aromatics (benzene type):

1. Benzene (C_6H_6)

2. Toluene (C_7H_8)

3. o-Xylene (C_8H_{10})

4. m-Xylene (C_8H_{10})

5. p-Xylene (C_8H_{10})

6. Ethylbenzene (C_8H_{10})

7. n-Propylbenzene (C_9H_{12})

8. i-Propylbenzene (C_9H_{12})

9. 1,2,4-Trimethylbenzene (C_9H_{12})

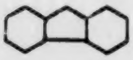
10. 1,3,5-Trimethylbenzene (C_9H_{12})

(List continued on following page)

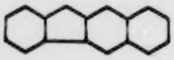
Polycyclic aromatics:

Since one and the same compound among the polycyclic aromatics often has several names, a simplified structural formula is given in addition to the numerical formula.

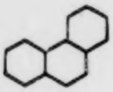
1. Fluorene ($C_{13}H_{10}$)



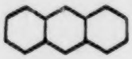
2. 2,3 Benzofluorene ($C_{17}H_{12}$)



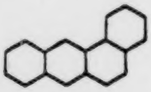
3. Phenanthrene ($C_{14}H_{10}$)



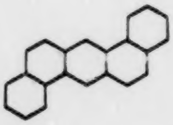
4. Anthracene ($C_{14}H_{10}$)



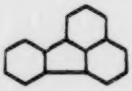
5. 1,2-Benzanthracene
   Benz(a)anthracene ($C_{18}H_{12}$)



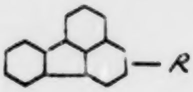
6. 1,2,5,6-Dibenanthracene
   Dibenz(a,h)anthracene ($C_{22}H_{14}$)



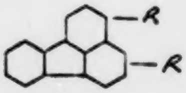
7. Flouranthene ($C_{16}H_{10}$)



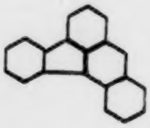
8. Alkyl-fluoranthene ($C_{16}H_9-C_nH_{2n+1}$)



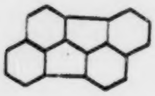
9. Di-alkyl-fluoranthene ($C_{16}H_8(C_2H_{2n+1})_2$)



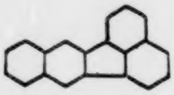
10. 3,4-Benzfluoranthene
    Benzo(b)fluoranthene ($C_{20}H_{12}$)



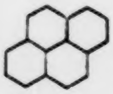
11. 10,11-Benzfluoranthene
    Benzo(j)fluoranthene ($C_{20}H_{12}$)



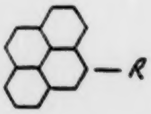
12. 11,12-Benzfluoranthene
    8,9-Benzo(k)fluoranthene ($C_{20}H_{12}$)



13. Pyrene ($C_{16}H_{10}$)



14. Alkyl-pyrene ($C_{16}H_9-C_nH_{2n+1}$)



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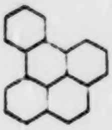
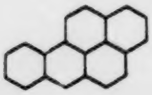
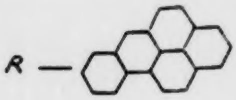
15. Benzo(e)pyrene ($C_{20}H_{12}$)



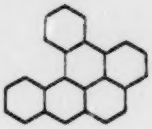
16. 4,5-Benzo(a)pyrene
8,9-Benzo(a)pyrene ($C_{24}H_{14}$)
9,10-Benzo(a)pyrene



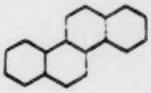
17. Alkyl benzo(a)pyrene ($C_{20}H_{11}$-C_nH_{2n+1})



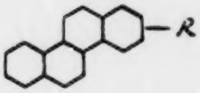
18. 1,2,9,10-Dibenzo(a,l)pyrene
4,5,6,7-Dibenzo(a,l)pyrene ($C_{24}H_{14}$)
6,7,8,9-Dibenzo(a,l)pyrene



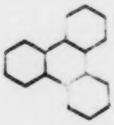
19. Chrysene ($C_{18}H_{12}$)



20. Alkyl-chrysene ($C_{18}H_{11}$-C_nH_{2n+1})

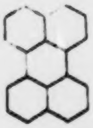


21. Triphenylene ($C_{18}H_{12}$)

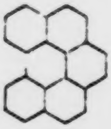


$R = -C_nH_{2n+1}$

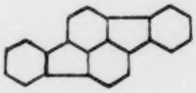
22. Perylene ($C_{20}H_{12}$)



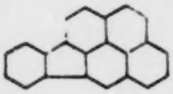
23. Benzo(ghi)perylene ($C_{24}H_{14}$)



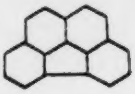
24. Indenol (1,2,3- cd)fluoranthene ($C_{19}H_{12}$)



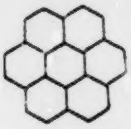
25. Idenol (1,2,3- cd)pyrene ($C_{22}H_{12}$)



26. Benzo(mno)fluoranthene ($C_{18}H_{10}$)



27. Coronene ($C_{24}H_{12}$)



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Oxidated hydrocarbons:

Aldehydes:

1. Formaldehyde (CH_2O)
2. Acetaldehyde (C_2H_4O)
3. Propionaldehyde (C_3H_6O)
4. n-Butyraldehyde (C_4H_8O)
5. i-Butyraldehyde (C_4H_8O)
6. n-Valeraldehyde ($C_5H_{10}O$)
7. i-Valeraldehyde ($C_5H_{10}O$)
8. Pivalaldehyde ($C_5H_{10}O$)
9. Acroleine (C_3H_4O)
10. Crotonaldehyde (C_4H_6O)
11. Benzaldehyde (C_7H_6O)
12. Salicylaldehyde ($C_7H_6O_2$)

Epoxides:

1. Ethylene oxide (C_2H_4O)
2. Propylene oxide (C_3H_6O)

Ketones:

1. Acetone (C_3H_6O)
2. Butanome-(2) (C_4H_8O)
3. 3-Methyl-butanone-(2)
   ($C_6H_{12}O$)
4. 1-Methyl-isobutylketone
   2-Methylpentanone-(4) ($C_6H_{12}O$)
5. Pentanone-(2) ($C_5H_{10}O$)
6. Pentanone-(3) ($C_5H_{10}O$)
7. 3-Buten-2-one
   Anisalacetone ($C_{11}H_{12}O_2$)

Alcohols:

1. Methyl alcohol (CH_4O)
2. Ethyl alcohol (C_2H_6O)
3. n-Propyl alcohol (C_3H_8O)
4. i-Propyl alcohol (C_3H_8O)
5. sec.Butanole-(1) ($C_4H_{10}O$)

Acetals:

1. Dimethyloximethane HCH $(OCH_3)_2$ ($C_3H_8O_2$)
   Formaldehyddimethylacetal
2. 1.1-Dimethyloxyethane
   Acetaldehydedimethalacetal ($C_4H_{10}O_2$)

Furanes:

1. Furane (C_4H_4O)
2. 2.5-Dimethylfurane (C_6H_8O)

Phenols:

1. Phenol (C_6H_5OH)
2. c-Cresol ($C_6H_4(CH_3)OH$)
3. m-Cresol ($C_6H_4(CH_3)OH$)
4. p-Cresol ($C_6H_4(CH_3)OH$)

Traces:

5. 2.4-Dimethylphenol ($C_8H_{10}O$)
   2,4-Xylanene
6. 2.5-Dimethylphenol ($C_8H_{10}O$)
   2,5-Xylenene
7. 3.5-Dimethylphenol ($C_8H_{10}O$)
   3,5-Xylenene
8. 2.3.5-Trimethylphenol ($C_8H_{10}O$)

3.2. Automobile Exhaust Gas Emission

These gases, vapors, aerosols and solids, which, in addition to other as yet unidientified components, comprise the automobile exhaust gas emission, escape via:

1. crankcase emission;
2. vaporized fuel from gas tank or carburetor; or
3. incompletely combusted or non-combusted hydrocarbon mixtures from the exhaust.

The percentage of the separate components varies constantly, since it depends on vehicle type, operating and maintenance condition, and engine equipment, as well as on fuel composition. It is obvious, therefore, that emission values or rates pertain only to those materials which are emitted constantly and in large quantities, and can be measured easily. Within any given test cycle, the most frequent measurements will be those of CO, NO_x, CH,SO_2, and solid components. In these, the internal combustion engines differ markedly from the Diesel engines, as is shown in the rough summary below:

Imission components	Internal combustion engines kg/1000 l fuel	Diesel engines kg/1000 l fuel
CO	274	7,1
NO_x	13,5	26,4
CH	24	16,4
SO_2	1,1	4,8
Solids	1,4	13,2

3.3. Automobile Exhaust Gas Imission*

Air polluting substances originating from motor vehicles will be defined as automobile exhaust gas imission when they have left their source and have entered the biosphere. Meteorological factors influence the composition of this imission, resulting in additional newly-formed compounds. Vertical and horizontal air movement determines the concentration of imissions; active air exchange leads to a reduction, while weather situations with little air movement lead to a significant increase in concentration. It may be assumed that in densely populated areas, high-rise buildings (reduced air exchange) will a priori produce local climates with a low exchange factor.

4. Health Damage Due to Automobile Exhaust Gas Imission

The detrimental effects of automobile exhaust gas imissions are due to:

1. the toxicity inherent in their noxious components;

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*Translator's note. The author distinguishes automobile exhaust gas emissions at the source and emissions in the atmosphere, using the German "Emission" and "Immission", respectively, as noted in Section 3.3. These terms are translated as "emissions" and "imissions", respectively.

2. synergy of several noxious components;

3. secondary atmospheric conversion into newly-formed noxious components.

Imissions show higher concentrations under unfavorable climatic conditions — so-called smog conditions — which lead to a dramatic rise in cardiac, circulatory and respiratory illness, as well as to a higher mortality, involving chiefly the elderly and debilitated. While it is easy to recognize these acute and sub-acute effects of such high imission concentrations, it is very difficult to evaluate the chronic effects of the pollutants constantly present in lower concentrations. These are inhaled for years — sometimes a lifetime — without an immediate threat to survival. They can, however, threaten human health, impair the physical and psychological effectiveness and severely affect the well-being of the population.

4.1. "Health Damage"

Health damage due to automobile exhaust gas imission can be said to have occurred when the resulting organic or functional changes significantly exceed the natural variation of organ forms or functions. This encompasses all clinically significant damage to organs and organ systems, as well as irreversible changes in vital physiological functions. It also encompasses all statistically significant changes in physiological or biochemical functions which are reversible, so long as care is taken to establish that the statistical significance of a deviation from the norm is medically also significant. Problems arise in the case of those functional changes which, after an initial significant change from the norm, later revert to a normal range, due to compensation on the part of the organism, while the stress due to the toxic substance persists. It is just in those cases that we must not regard a certain toxic substance as tolerable by an organism simply because a given parameter has re-achieved a normal value: such an adaptive or defensive mechanism can very well represent more stress or decreased resistance against another noxious substance.

"Health damage" also refers to the effects of irritants or substances affecting the mucous membranes (oxidants). Although these are neither as important as organic illnesses nor the cause of immediate health damage, they can still impair well-being indirectly through psychosomatic disturbance. They cause local irritation of the mucosa, the eyes and the respiratory passages, and can be associated with pain, tear secretion and coughing. These irritations due to imissions are primarily a subjective phenomenon; basically, they cause unpleasant sensory reactions and their consequences, which temporarily but considerably restrict psychological and physiological efficiency, and reduce attention span and the ability to concentrate. If these effects are chronic, they can cause reversible or irreversible changes and illnesses of the respiratory passages and the eyes. Here the transition from impaired well-being to health damage is especially clear.

5. Establishing Maximum Imission Values

The present report is a survey of the international literature; it will also use current information in an attempt to propose maximum imission values, so that health damage to the population, particularly children, the aged and the sick, can be avoided.

5.1. Basis for Determining Parameters

The large number of individual components of automobile exhaust gas imission, on the one hand, and the constant variation in their proportion, on the other, might lead to the conclusion that it is impossible to establish a single parameter for this mixture. This study, therefore, will not attempt to derive a parameter for automobile exhaust gas imission in general; it intends to propose, rather, several parameters for the relevant toxic individual components.

A survey of the international literature on relevant toxic components indicates that either no parameters exist, or that their values vary greatly from one country to another. Not only are there great differences in the values given for individual components, but their very toxicity itself often receives diametrically opposite evaluations. An explanation for the great differences or even inversions of toxicity evaluations in the determinations of parameters by various industrial nations can be found in different testing methods and different weighting of results. Quite different aspects, for instance, were applied in the evaluation of experimentally and epidemiologically established findings. The relevance of data pertaining to human health varies greatly between countries, and leads to different parameters for one and the same material. Moreover, it is not only scientific data which enter into these evaluations, but also different approaches to the concept of health itself and the definition of its essential attributes, as well as judgments on the need to protect various areas of good health in general.

Basically, four areas contribute to the establishment of parameters:

1. industrial health investigations and observations;
2. animal experimentation;
3. human experimentation;
4. epidemiological studies.

Taking these areas into consideration, we attempted, first of all, to use the international literature and our own experience in order to establish long- and short-term MIK (Maximum Imission Concentration) values for single components. In this we deliberately left economic viewpoints out of the picture; the proposed parameters are to be regarded as the result of scientific considerations only.

5.2. Definition of Maximum Imission Concentration MIK Long Term and MIK Short Term Values

The MEC long term value (MIK_D) is the average over a 24-hour period, in which the MIK short term value (MIK_K) may have been exceeded during only 5% of the 24-hour interval. This 5% excess over the MIK_K value may last only 30 consecutive minutes, and must be followed by a recovery period of at least 120 minutes, during which the average value will correspond to the MIK_D value.

The MIK short term value (MIK_K) is defined as the average of a 30 minute period during which an excess beyond a ceiling specific for the component in question is permitted for only 5% (90 seconds) of the half-hour interval.

6. Discussion of Specific Components or Groups of Components of Automobile Exhaust Gas with Proposals for Imission Parameters

6.1. Carbon Monoxide

6.1.1. Preliminary remarks

According to American estimates [1] for the year 1968, automobile exhaust gas contributes approximately 60% to the total CO emission in the U. S.A., while industry contributes only about 11% throughout the country. During 1969, the annual CO emission in the Federal Republic of Germany was quoted at approximately 8 million tons, corresponding to about 40% of the total emission of noxious material. Based on presently available data and the projection of the Federal Government [2], the CO emission for 1972 can be estimated at 4,100,000 tons, i.e., 51%. Private cars and vans (internal combustion engines) contribute 3,820,000 tons — 93%; trucks (Diesel) — 190,000 tons, 2.5%; and buses (Diesel) — about 13,000 tons, 0.3%. According to estimates of the State of Nordrhein-Westfalen [3], internal combustion engines produce approximately 274 kg CO per 1000 liter fuel, Diesel engines only about 7.1 kg/ 1000 l.

Further sources are, particularly, the iron and steel industry with its furnaces, the ceramic industry with its kilns, brick factories, and the chemical industry with its variety of installations, as well as domestic heating equipment. Besides these stationary sources, the constantly increasing traffic density, especially in such thickly populated areas as the inner cities, is of the greatest significance for health aspects of the atmosphere (Fodor, [4]). Measured directly at the exhaust pipe, CO concentrations for internal combustion engines — depending on vehicle type, engine condition, etc. — range from 1 to 10 vol. %, corresponding to 10,000 - 100,000 ppm. Although these concentrations are reduced by a factor of 10^2 even .5 m from the opening of the exhaust pipe, the 24 hour average CO imission values lie between 5 and 30 ppm, and the 30 minute maximum imission values can reach even 50 ppm, with brief levels of 300 ppm a possibility.

6.1.2. General effects

Carbon monoxide is a highly toxic, non-irritating, colorless and odorless gas which is not perceived by any human senses. It penetrates undetected into the lung alveoli, passes through the tissue-blood membrane, gets into the blood and, due to its high affinity for hemoglobin, forms a bond with its bivalent Fe-atom. There it displaces the loosely-bonded oxygen competitively and thereby reduces the oxygen-carrying capacity of the blood. If CO-containing air is breathed long enough, an equilibrium is established between the CO content of the blood and that of the surrounding air. This equilibrium is determined by the mass effects law, as well as by a constant characterizing the affinity relationships of CO and O_2 to hemoglobin. The affinity of CO for human hemoglobin is 210 times that of oxygen; given sufficient exposure time, even relatively low concentrations lead to oxygen deprivation in the tissues. This CO-caused hypoxidosis affects, first of all, and severely, those organs with the highest oxygen requirements. Among these, in addition to the heart, is first of all the brain; although only 2% of the body weight, the brain consumes 20% of its oxygen supply (Fodor and Winneke [5]). Individuals suffering from heart, circulatory or brain-circulatory deficiencies (the elderly), therefore, are especially endangered by CO exposure (Fodor et al. [6]).

COHb concentrations of 60% are fatal, 40 - 50% cause severe toxic symptoms with loss of consciousness and collapse, 20 - 30% cause headache, dizziness and loss of alertness. Low COHb values of approximately 10% cause no obvious toxic symptoms, but they are damaging to health since they affect psychological and physical capacity. Estimating the effects of CO can be done only by means of the COHb values, which depend on the CO and O_2 content of the air, the exposure time, and the inhalation/minute volume (Schlipköter [7]).

In man, the saturation equilibrium between low CO values in the air and the COHb content of the blood (given a sufficiently long exposure and a base level of 0.5% COHb in the blood) can be expressed by the simplified formula (Goldsmith and Landaw [8]):

$$\% \text{ COHb} = 0.16 \times \text{ppm}$$

According to this formula, for instance, 10 ppm in the inhaled air — given sufficient exposure — would lead to 2.1% COHb, and 20 ppm — to a blood level of approximately 3.7%.

In another experiment by Peterson and Stewart [9], human volunteers were exposed to CO concentrations from 25 to 500 ppm, for periods ranging from 30 - 480 minutes; the CO content of their blood was measured at regular intervals without necessarily waiting for equilibrium conditions to be achieved. The CO content can be represented by the logarithmic linear equation:

$$\text{Log } \% \text{ COHb} = 0.85753 \text{ Log CO} + 0.62995 \text{ Log } t - 2{,}29519$$

or

$$\% \text{ COHb} = \frac{\text{CO}^{0.86}\ t^{0.63}}{197}$$

The equations describe the relations between exposure time t (in minutes), CO concentration (in ppm), and the resulting COHb content of the blood (in %) of persons at rest. Therefore, the exponent 0.63 may essentially be a function of the inhalation per minute volume, while the exponent 0.86 may reflect the affinity coefficient

(Fodor,[10]). Another linear equation (Forbes et al. [11]), as well as a modified exponential model (Coburn et al. [12]), and the above logarithmic linear equation were compared as to their predictability [Knelson, 13]. As expected, the simple linear relationship showed good agreement with the data for periods up to 4 hours. The same holds true for the logarithmic model. Therefore, these models are not quite suitable for long exposures (as in public health inquiries), whereas the exponential model (which agreed very well with the COHb values obtained over exposures of more than 24 hours) permits reliable predictions of the acquired COHb content of the blood.

It is certain that it is the hemoglobin which stores most of the CO; it is the blood, therefore, which contains most of the CO absorbed. According to Coburn [14], only 10 - 15% are found elsewhere. The presence of other specific bonding sites is decisive for the absolute amount of CO contained in the tissues. The myoglobin in muscles, for instance, is such a site and can, therefore, store significant amounts of CO in this tissue. Here, too, oxygen and CO compete for bonding sites, similar to the situation in hemoglobin. Cytochrome may play a similar role, since here, too, CO and oxygen interact in a like manner. The quantities involved here, however, are not significant.

CO undergoes no change or decomposition in the organism; it remains in the body without being metabolized until it can be released again through the lungs. This occurs when continued exposure results in a diffusion equilibrium, and CO is released in amounts proportional to those absorbed; or when the CO concentration in the inhaled air drops such that the CO is exhaled until a new diffusion equilibrium is reached or until it is excreted completely. In these cases, it is the CO which, in turn, is replaced by oxygen.

6.1.3. Public health aspects of results in man

The range of CO values (= 10%) which do not produce decisive toxic symptoms is relevant to the public health aspect. Even recently, it was generally held that CO values of that order can be tolerated for years without affecting human health (Borbely [15]). Today, however, the assumptions are that even values of CO below 10% interfere with the functioning of:

1. the central nervous system;
2. the cardiovascular system,

according to Schlipköter [16].

6.1.3.1. Effects on central nervous system

In scanning the literature, it can be seen that as early as 1944, McFarland et al. [17] detected a slow decrease in efficiency in the presence of 4.5% COHb; it showed itself in a loss of brightness-differentiation ability.

In later investigations of the function of the central nervous system, similar results were obtained under CO stress. Halperin et al. [18] in 1959 obtained measurable decreases in visual perception using levels of 4 - 5% COHb and their effect on the visual limits; the effect increased with rising COHb concentrations. Also this experiment demonstrated the lag between elimination of CO from the blood and the recovery of visual capacity from its detrimental effects. Beard and Wertheim [19] tested the capacity to distinguish elapsed-time intervals under CO stress, and could reproduce losses in that function with COHb values as low as 2 - 2.5%. Beard and Grandstaff [20] reported the results of another test of time perception under CO stress in 1970. The subjects were asked to estimate time intervals ranging from 10 - 30 seconds. Ten second intervals were not affected by CO; judging the 30 second intervals, however, showed a significant loss associated with dosages as low as 50 ppm CO over a period of 64 minutes. The same paper reported investigations by Wertheim [20] on the effects of CO exposure on visual perception; four tests were run at concentrations of 50, 150, and 250 ppm and a total exposure time of 1 hour per test day. Visual perception was consistently affected in three of the four tests. The COHb values in these experiments were between 3 and 7.5%. Horvath [21] found that a 2 hour exposure to 111 ppm CO resulted in a significant decrease in visual acuity.

Fodor & Winneke [5] tested the effect of a 5 hour exposure to 50 ppm CO on the resistance to monotony and on psychomotor capacity. The test battery comprised attention capacity, flicker frequency, tachistoscope tests and psychomotor tests. Exposures to CO of 80 - 125 minutes resulted in objectively measurable losses in attention capacity at concentrations of approximately 2.5% COHb, which agrees well with other results in the literature. When the test was continued, these losses disappeared, although the COHb levels were increased up to 4.3%, which raises the possibility of a compensatory regulatory mechanism. Flicker frequency determinations and the tachistoscope test showed no CO effects, nor was psychomotor capacity demonstrably affected by COHb levels of around 5%.

Knapp et al. [22] reported tests on vigilance performance and central nervous system functions under the influence of 50, 100, and 150 ppm CO for a 2 hour exposure time. COHb values of the subjects reached corresponding levels of 3%, 5.4% and 7.6%. They were given 1 1/2 hour long attention tests in which they had to respond to random changes in signals offered at unpredictable intervals. Paired tones with a regular signal separation of 1.1 second were offered, the second tone being slightly but randomly softer. This should have brought about the classical situation in which the central nervous system gradually produces changes in its activity, the so-called expectation or readiness potentials. These were recorded by electroencephalograms; spontaneous activity was separated out by computer analysis, and the amplitude of the rise and drop in potential evaluated. The results were as follows: The number of missed — i.e., not heard — changes in signal rose significantly, depending on the rise in concentration. The decrease in capacity observed under controlled conditions during the second half of the experiment could be accelerated by CO exposure and was paralleled by the degree of exposure. The readiness potentials, with regard to the criteria being measured, showed a considerable decrease. Here, too, there was a linear relationship between degree of exposure and the significant changes of the readiness threshold in the EEG, as expressed by decreased amplitudes of the rise and drop of the potentials.

Stewart et al. [23] obtained results of a different nature. They tested the influence of CO concentrations from 1 - 100 ppm in terms of the parameter of elapsed time estimation. During an exposure of 8 hours, COHb levels of 11 - 13% were reached; but neither subjective nor objective symptoms of any negative effects could be observed. According to those authors, COHb values of up to 31.8% did not affect the capacity to estimate elapsed time intervals. Mikula [24], using 3 hour exposures of up to 250 ppm CO, also found no changes in tests of psychomotor skills, elapsed time estimation, tests of signs and test of vestibular function.

The relevance of these contradictory results to complex behaviors, especially driving motor vehicles, is difficult to judge. It should be noted to begin with, that Mikula and Steward obtained results in a group situation where possible elements, such as competition and other stimuli, may have overcome the effects of CO exposure, while Beard, Wertheimer and others obtained results in isolated cubicles in which boredom and fatigue could have accentuated the effects of CO.

Driving a car in traffic, however, may certainly bring about situations not immediately within the expectations of a driver. This makes it all the more necessary to consider the CO produced impairment in attention and the interrrlationships between extraneous factors (as, for instance, noise, fatigue, boredom, and other distractions) and the tests under CO exposure. The additional effect of such variables was illustrated by Forbes [25], who observed driver skills under CO exposure (COHb values up to 50%). The subjects could concentrate fully on the tests and accomplished the tasks, although they were near collapse and felt unable to drive a car. Ray and Rockwell [26] investigated real driving performance under low CO concentrations. In this study, they went outside the laboratory, allowing three young men to drive a car during the night on a highway while under the influence of 10 - 20% COHb. In order to maintain these COHb concentrations, additional CO was supplied during the actual driving. At COHb levels of 10 - 20%, the latent period before reacting to brake lights or speed changes increased. Maintaining a 65 mph speed, staying in the proper lane, and keeping a constant distance of 200 feet from the car ahead were also impaired. The test demanded simultaneous responses to several stimuli; in the authors' opinion, this prevented the driver from concentrating on one aspect for extended periods of time. Grudzinska [27] observed 60 workers who were subject to chronic exposure of no more than 100 ppm CO at their place of work; their EEG's differed from those of a control group of 30 workers doing similar work who were not exposed to CO. In the exposed group, the COHb level was 7% (for 11 subjects the level exceeded 10%); in the control group — 3%. Grudzinska observed a slightly higher proportion of the flat EEG curves with a low alpha rhythm in the exposed group. Bender et al. [28] tested the impact of 100 ppm CO on psychological functions. The tests were made under a COHb concentration of 7.25%. Significantly lower performances were obtained for visual perception (letter recognition), psychomotor skills (hand and finger dexterity in peg-board tests), learning (10 nonsense syllables), and a partial test from the Intelligence Structure test by Amthauer with highly verbal associations. Schulte [29] carried out a number of behavioral tests and came to the conclusion that reduced brain function begins with approximately 5% COHb.

6.1.3.2. Effects on cardiovascular system

In regard to the effect of CO on the cardiovascular system, Ayers et al. [30, 31] were able to demonstrate changes in the alveolar-capillary gas exchange, the circulation, and the myocardial metabolism in ill as well as healthy subjects. These investigations lead to the impression that persons suffering from heart disease or emphysema may be particularly sensitive to CO stress leading to COHb of approximately 5%. The experiments were carried out only with very short exposures at very high concentrations (4000 ppm for 5 - 7 minutes). It is, therefore, difficult to compare the observed results with those of equilibrium conditions or longer exposures. Knelson [30], however, chose relatively long exposure time (4 hours) at low CO concentrations (100 ppm) in connection with measuring cardiac response to near-maximum physical stress. Here, the COHb values rose to 5 - 9%. It could be shown that, with equal cardiovascular stress, total physical capacity was less under CO exposure than under normal conditions. On the other hand, younger subjects (25 - 36 years old) evinced higher cardiac rates under stress during exposure, which suggests a higher capacity for myocardial stress under similar work loads. Older subjects (41 - 60 years old) had abnormal EKG's more frequently; in two subjects, arhythmic symptoms were found after exposure. The index of expulsion time for the left ventricle, as well as the index of the preceding interval, also worsened significantly in older subjects after exposure. From these observations, the authors conclude that exposure to low CO concentrations can exacerbate myocardial ischemia, impair myocardial function, and increase the development of arhythmic symptoms during physical stress for a large part of the population. Low CO concentrations especially affect those who already suffer from diseases of, for instance, the coronary vessels or emphysemas.

Brody and Coburn [33] not only calculated theoretically, but also proved experimentally, that under conditions of arterial hypoxemia (the result of abnormal blood exchange in the lungs or a venous-arterial shunt), tissue hypoxia due to increased COHb (10%) can rise significantly; and that persons with abnormalities of that order, therefore, are confronted by special risks during CO exposure.

6.1.3.3. Adaptation with long term exposure

The question of adaptation to the chronic effects of exposure to low concentrations of CO is a recurring problem. Animal experiments showed that a 3-month exposure to low concentrations can lead to a rise in the hematocrit, hemoglobin content, and red blood cells, as well as to enlargement of the heart (Ehrich [34]). Astrup [35] found that hemoglobin concentration showed an initial rise, but stabilized later — only to rise again when the CO concentration was increased once again.

Wilks [36] acclimatized dogs to CO dosages of 800 - 1000 ppm and recorded an increase in red blood cells, hemoglobin and blood volume. When CO exposure was renewed, equilibrium conditions produced no changes in CO saturation when compared to non-acclimatized animals. In human experimentation we have only one study, in which Killick [37], using herself as subject, examined the results of long-term, intermittent exposures to 190 - 450 ppm CO over a six month period. The COHb levels used in this study, however, were obtained by means of a very inaccurate method; the author's opinion that an adaptation had indeed occurred can be accepted only to a limited degree. All in all, the data available for physiological adaptation of man to CO permit no definite conclusions; adaptation to a certain degree seems possible, but the mechanism is unclear.

6.1.4. Animal experimentation

In warm-blooded animals, the effects of high CO concentrations lead to shortness of breath, weakness, staggering, lying on the side, convulsion, and finally to death. The sensitivity to CO is species-specific and shows large individual variation. This is, essentially, due to the varying affinity of CO for the hemoglobin of different animal species (Fodor and Winneke [38]).

Even with slight CO intoxication, hypoxemia plays a considerable role, although the decreased O_2 supply to the tissues cannot be the sole direct cause for many of the steps known today as leading to CO poisoning or impairment.

The extent of oxygen deprivation in tissues can be measured with electrodes by means of "least-point" measurements. In a very extensive study, Zorn [39] measured the partial oxygen pressure in the brain and in the liver during sub-toxic CO concentrations. Rats, rabbits, and cats were exposed to CO concentrations ranging from 80 -

720 ppm; exposure periods and the resulting COHb saturation were chosen such as to largely avoid the secondary consequences of hypoxemia, e.g., metabolic acidosis and changes in capillary circulation. At COHb values between 3% and 30%, Zorn found that the decrease in partial oxygen pressure in the tissues was linearly inversely proportional to the increase of CO saturation in the blood. He showed, furthermore, that after reaching a steady state (diffusion equilibrium) at values between 6 and 8% COHb, the pO_2 decreases steadily for 20 minutes, and that an increase in pO_2 can be expected only 5 - 20 minutes after the end of exposure. During the saturated phase, as well as during the excretory phase, the gradient of pO_2 to COHb change depends on the blood supply to the tissue under examination. This gradient, therefore, was compared to the appropriate at-rest value of O_2. The resulting quotient ranges between 1.6 - 2 for animals at rest, shows less favorable values in older animals, and can be decreased by even slight muscular effort. This clinically well known fact was again demonstrated in the present study for even very low COHb values (5%). In some areas of the brain with poor capillary blood supply, a COHb value of only 8% decreased the pO_2 by 8 torr to below the critical value of 1 torr. In summing up this study, it can be asserted that even very low CO concentrations, which raise the COHb to only 2.5%, will cause decrease of the pO_2 in the tissues -- resulting in an inhibition of the functions, particularly of such vital organs as brain or liver.

These measurements of tissue hypoxemia could corroborate the findings of many other investigations. The jaw muscle of albino rats, for example, demonstrated, upon 10 minute exposure to 250 - 1250 ppm CO a decrease in the amplitude of muscular contractions which was directly related to concentration (Malorny [40]). In another experiment (Malorny [41]), it could be shown that in a stress situation calling for immediate mobilization of energy reserves (swimming attempts by rats), physical capacity after 1 hour of CO exposure to 300 ppm (8 - 13.5% COHb) and 500 ppm (20 - 28% COHb) was significantly less than that of a control group. These effects could be demonstrated even after a 2 hour recovery period when the COHb was practically undetectable. Supplemental swim tests were run on mice in concentration ranges below 300 ppm. Here, too, there was CO stress during the swimming attempts, and a similar loss in capacity could be demonstrated. In "digging tests" with golden hamsters (Schargus [42]), a striking drop in the amount of sand removed could be obtained in 50 hamsters by the effects of a four hour exposure to 100 - 50 ppm CO. Malorny et al. [43] described the effects of long term low CO exposures: the pronounced locomotor drive of white mice, exposed for 14 hours to a CO atmosphere of 160 ppm and then allowed 3 hours on the treadmill, was reduced to one quarter of the distance covered by a control group; at 84 ppm, the lost was 50%, and at 55 ppm — one third. If use of the treadmill and CO exposure started simultaneously, a loss in output could be registered as of 100 ppm; between 50 and 75 ppm, the authors observed frequent escape motions, especially during the first hour, which was considered the crucial symptom in terms of escape attempts; from the second hour on, running movements were paralyzed and efforts frequently reached a low point after the end of exposure.

A series of results can be attributed to the proven hypoxia in the brain. In a long term experiment using intermittent exposures (10 weeks, 15 hours per night from 5 p.m. to 8 a.m., circulating air-CO mixture of 150 ± 10 ppm), Malorny et al. [43] showed learned reaction losses after CO exposures. Rats had been trained to avoid an electric shock by leaping on a freely suspended perch as soon as a light-and-tone signal was given. The unconditioned and conditioned response was tested twice a week, 6 hours after the end of exposure to CO, at which time no more COHb was present in the blood of the animals. After 4 weeks, 40% of the CO exposed animals had unlearned the response; moreover, a striking loss of activity and increasing indifference could also be observed. After 10 weeks, the whole CO group had totally lost the flight response. The control group retained both responses in full. The interference with such behavior lasted a considerable period after CO exposure, which suggests cerebral changes. Zorn [44], continuing this study, could also demonstrate significant losses in learning ability of CO exposed animals. Wistar albino rats were exposed 5 times per week for 8 hours at a time to a CO concentration of 150 ppm, resulting in a COHb value of 10 ± 3%. After adequate CO ventialtion, the animals were taught a condition flight response, and the results tested some time later. Compared to the control animals, the CO-stressed animals evinced significantly longer learning times, frequent errors, and a tendency to stuporous or anxious behavior. In a series of tests run by Beard and Wertheim [19], a scheme of differential rewards for delayed reactions, i.e., for estimating elapsed time, was used with rats. The animals were taught that pressing a lever was rewarded only when certain intervals were maintained. CO exposure affected the animals' capacity for time estimation very quickly. With a minimal delay of 30 seconds required for the reward, even 11 minutes of a 100 ppm exposure could be shown to be detrimental. Sonntag [45] could prove the influence of CO on reaction latency in rats and guinea pigs. When reaction latency (i.e., the interval between applying the afferent sensory stimulus and the motor response of the flight reaction) was measured even in a low range of COHb concentration of 10% administered intraperitoneally, the unconditioned response was delayed by 15 ± 4.5%.

Xintaras et al. [46] examined the evoked cortical potentials of rats under the influence of 50 and 100 ppm CO and varying exposure periods. Evoked potentials are regarded as a relatively direct measurement for the degree of central nervous system reactivity. Using a 1 hour exposure to 50 ppm (corresponding to about 2% COHb), the authors could show significant changes in the potentials, which increased proportionally after 2 hours, and showed definite cumulative effects after repeated exposures. A period of 48 hours was required to regain the initial values. After a 24 hour exposure to 250 ppm CO, rats showed changes in their sleep and wakefulness pattern (Fodor et al. [47, 48, 49]). Longer exposures of more than 96 hours in the same concentration range yielded similar results (Colmant [50]).

Lewey and Drabkin [51] exposed dogs for 11 weeks, during 5 3/4 hours on 6 days per week to 100 ppm CO, resulting in a COHb level of

20%. The EEG and the functioning of the peripheral nerves showed no change; but there was severe interference with posture and gait. After exposure, morphological examination of the nervous system revealed cortical damage. The control animals showed no such changes. Moreover, the authors found histological changes in the white matter of the cerebral hemispheres, the globus pallidus and the cerebrum.

Lindenberg et al. [52] found that dogs exposed chronically or intermittently for 6 weeks to 100 - 50 ppm CO developed distensions of the lateral ventricle and a certain rearrangement of the glia, which can be regarded as a preliminary stage for cerebral pathology. They could not demonstrate any necroses or demyelinations.

The influence of low CO concentrations on the fetus was investigated by Astrup et al. [53] because of the fact that women who smoke bear children whose weight is, on the average, 200 grams below the norm. Using rabbits exposed to CO concentrations of 90 and 180 ppm (corresponding to a COHb of 8 - 10 or 16 - 18%) during their pregnancies, he obtained lower birth weights, a greater number of stillborn animals, and a greater number of deaths within the first 24 hours after delivery. Some of the newborn animals from exposed rabbits were born without legs, implying teratogenous effects of CO.

In addition to these findings, which are largely due to oxygen deficiency, CO exposure results in a whole series of symptoms requiring other explanations. Rozera and Fati [54], using rabbits exposed for several days to 100 ppm CO, obtained a decrease of acid and alkaline phosphatases in red blood cells. This effect was not obtained in animals subjected merely to oxygen deprivation. Fati et al. [55], using rabbits exposed to 100 ppm CO, also found a loss in phosphoglycomutase activity of erythrocytes, in contrast to the control animals under only oxygen deprivation. Barrios [56] investigated the arching reflex of the cat, ordinarily inhibited noradrenergically by the spinal cord. Under CO stress, the phenomenologically opposite, excitatory effect was obtained. Dopa can activate this inhibitory system of the spinal cord. Barrios first exposed cats to a high concentration of 1330 - 1630 ppm CO, then had them breathe, first of all, pure oxygen (plus 3% CO_2 for quicker elimination of the CO effects) and then room air during the recovery phase; at this point, the experimental animals were injected with dopa, but not the control animals. The excitatory effect of CO could be blocked by dopa, a result not achieved by breathing pure O_2 (plus 3% CO_2). Thus, the activity of enzymes catalyzing noradrenalin in the body seem to be reduced by even low CO concentrations. This is corroborated by the circumstance that these enzymes — similar to those in red blood cells — are bonded to heavy metal ions; in both instances, CO has a parallel negative influence on their activity. The enzyme cytochrome P-450, which bonds CO and is inhibited by CO in its function, plays an essential role in the microsomal enzyme activities. Rondia [57] could demonstrate the effect of insignificant dosages of 60 - 150 ppm CO over 2 - 7 days on the enzyme activity in the livers of Wistar rats. He examined the activity of aromatic hydroxylase, which rose slightly but significantly as early as the second day. If the oxygen requirements of the liver were raised artificially (with benzopyrene or methyl choranthrene), a 40% decrease of aromatic hydroxylase (compared to that of the equally induced control animals) was found. These experiments also showed that the total protein content and the amount of cytochrome P-450 in the liver are not changed by CO, and the effects observed are not due to oxygen deifciency.

Bauer [58], investigating the composition of serum and brain tissue proteins, found that these changed in rats exposed to 450 ppm CO (8 hours) and 250 ppm (65 hours). In the test using 450 ppm, alpha-2-globuline increased, which was interpreted as a stress reaction. Longer exposures at 250 ppm produced a tendency to lower the albumin and increase the slowly-transporting globulines. After repeated long term exposures (11 weeks, 160 ppm, 7 - 8 hours per day) considerable reduction of albumin and increase in gamma globulines could be demonstrated. This was attributed to liver damage, and histologically confirmed. In analyzing brain tissue proteins, relatively low CO concentrations caused an increase of the fast albumin fractions and a loss of the so-called brain-specific proteins, a sign of increased diffusion of serum proteins into the cerebral paranchyma. The cause can be assumed to be impairment in the function of the brain-blood interface.

Astrup et al. [59] made a significant contribution to the problem of the atherogenous effect of low CO concentrations. When rabbits were fed cholesterol and exposed continuously to 180 ppm CO (15% COHb) for 10 weeks, they developed 2.5 times greater cholesterol deposits in the aorta than the control animals that had also been fed cholesterol. This experiment was repeated several times, and the results were reproducible. Animals subjected to interrupted exposures (10 weeks, 8 hours a day) showed even 5 times greater cholesterol deposits in the wall of the aorta than the control rabbits. Lipoid increase was essentially a function of the composition of the respired air, for CO stress and hypoxia produced similar negative results, while hyperoxia brought on a decrease of the deposits. CO stress per se, with a COHb value of 9 - 10%, and without the animals being fed any cholesterol, also produced arterial damage in the form of endothelial hypertrophy and proliferation as well as focal edemas lying beneath the intima. These lesions could not be distinguished from spontaneous arteriosclerosis occurring in rabbits. CO exposures of 180 ppm over a 2 week period with COHb values of 16 - 18% produced edema under the endothelial cells; the normal folds of the endothelial membrane disappeared because of blisters beneath the cells; fluid entered and completely separated the endothelial cells from the basal membrane, the endothelium was torn, tiny hemorrhages and free aggregates of erythrocytes and thrombocytes could be observed regularly. The researchers believe that CO or hypoxia further atheromatosis by increasing the permeability of vessels for lipoproteins.

6.1.5. Summary and conclusions

Impairment of the oxygen transport system is the primary toxic effect of CO. Long term exposures can produce morphological changes in heart and brain. With 50 ppm, abnormal EKG's, mobilization of the glia, and enlargement of the lateral cerebral ventricles were found in dogs. Increases in the level of hemoglobin, of the hematocrit and of the number of red blood cells were also observed. At 100 ppm, enlargement of the right, and occasionally of the left, heart ventricle occurred, as well as degeneration of the heart muscle. Other animals developed disorders of posture and reflexes; cortical damage was found at autopsy. The effect of CO on the cardiovascular system suggests the possibility of adaptation. Short-term exposures at low CO levels showed effects on the central nervous system. Below 50 ppm CO, rats showed EEG changes and a deterioration in the time differentiation capacity.

Short term CO exposures affected the central nervous system, the cardiovascular and the respiratory systems. The effects on the central nervous system began at 2% COHb, and impaired the ability to estimate elapsed time, to discriminate brightness levels, as well as visual acuity, psychomotor efficiency and visual function.

Concentrations above 5% COHb lead to disorders of the cardiovascular system. The oxidative mechanism of the circulation is impaired, especially that of the myocardium. Persons with cardiovascular disease are, therefore, particularly endangered.

On the basis of the above study, a COHb value of 2.5% must be regarded as critical. It is reached in various ways; either by means of low atmospheric concentrations for extended periods of time, or high concentrations over short periods. Persons with a rapid metabolism and resulting high O_2 consumption are particularly sensitive — i.e., children, the sick, and people performing medium to heavy physical labor. Defining 2.5% COHb as the critical value is based on studies which demonstrated impairment of psychophysiological functions — under the control of the central and peripheral nervous systems — as well as of the cardiovascular system. Figure 1 summarizes the data on the effects of low COHb values on man. The sharply defined categories used in the above discussion do not represent the actual state of affairs, but were chosen merely to simplify the arrangement of the information. In reality, transitions between the various areas of inquiry are fluid indeed.

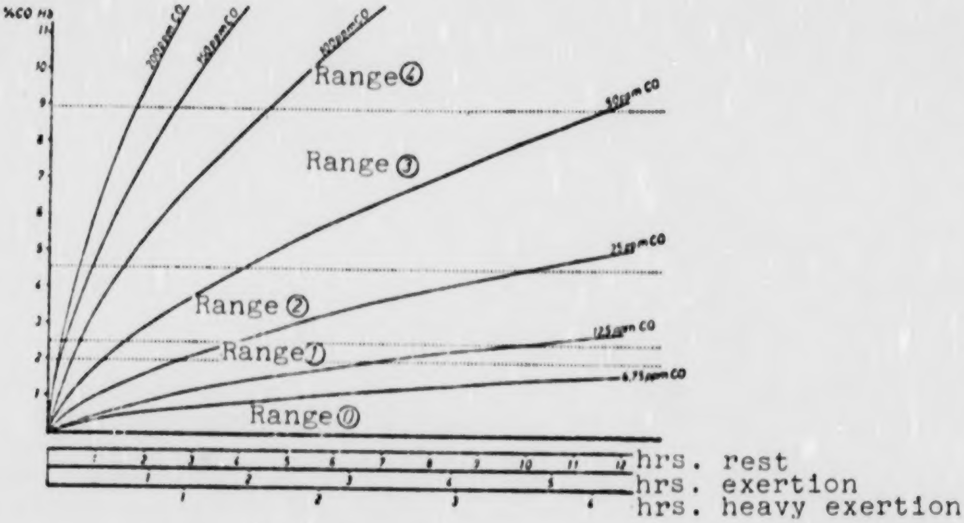

Figure 1. Schematic representation of COHb formation vs. degree and length of exposure during rest and varying amounts of exertion. Ranges are assigned to the COHb values along the ordinate

While COHb ranges of below 2% (range 0) are at present considered insignificant, range 1 (2 - 2.5% COHb) already produces losses in elapsed-time-estimation capacity, as well as slight but significant losses in vigilance. Range 2 (2.5 - 4.5% COHb) accentuates these symptoms in addition to losses in calculation, choice, and concentration responses. Moreover, perception tests showed losses in brightness discrimination, visual acuity, and flicker frequency. Range 3 (4.5 - 9% COHb) accentuates these symptoms, and is characterized by decreased perception rates, loss in short-range memory and manual dexterity; cardiovascular symptoms also appear. Range 4 (above 9% COHb), besides accentuating all the above objectives losses and symptoms, also produces the first subjective signs of intoxication, e.g., headache, etc.

On the basis of the above data, we propose a:

MIK — long term (MIK_D) of 10 mg/m^3 (9 ppm);

MIK — short term (MIK_K) of 35 mg/m^3 (32 ppm).

These limits may be exceeded for no more than 90 seconds up to 130 mg/m^3 (118 ppm) (90 seconds) (cf., p. 17, Section 5.2).

6.2. Nitrogen Oxides

6.2.1. Introductory remarks

The group of nitrogen oxides contains several gaseous compounds produced by the oxidation of nitrogen (N_2). They may be inorganic — frequently referred to as "nitrous gases" or, using metering terminology, as NO_x — or organic; the latter are produced under certain meteorological conditions by complex photochemical reactions between N-oxides, atomic oxygen, and hydrocarbons.

These latter compounds will be dealt with further on in Section 6.5 — "Oxidants", and are not discussed here.

Below, we shall discuss only those inorganic N-compounds which are of environmental significance, making only brief mention of the others.

First among the N-oxides is the colorless gas nitrogen monoxide (NO); it is fairly stable in certain temperature ranges, and forms — combined with atmospheric oxygen — the very unstable nitrogen trioxide (N_2O_3), the somewhat more stable, brownish nitrogen dioxide (NO_2), and the yellowish dinitrogen tetroxide (N_2O_4).

The relationship between nitrogen dioxide and dinitrogen tetroxide can be represented by the following equation:

$$2\ NO_2 \underset{\text{heating}}{\overset{\text{cooling}}{\rightleftharpoons}} N_2O_4$$

We need also to mention dinitrogen oxide (N_2O), as well as dinitrogen pentoxide (N_2O_5). The former is a fairly nonreactive gas without toxicological significance; the latter probably does not occur in the atmosphere at all. Toxicologically, NO and NO_2 or N_2O_4 are the most important nitrogen oxides.

Nitrogen oxide (NO) is a colorless and odorless gas which is easily soluble in water. In nature, it is largely formed by bacteria and can, therefore, be demonstrated even in uninhabited areas in concentrations of approximately 0.002 mg/m^3 (0.0017 ppm). In areas with heavy traffic, however, considerably higher values are obtained. This oxide is derived mostly from industrial combustion processes requisite to heat and energy production. Due to the endothermal reaction $N_2 + O_2 = 2\ NO$, nitrogen oxide is formed from nitrogen and oxygen at temperatures above 1000° C. Upon rapid cooling of the gases so formed — as in the case of exhaust gases — the reverse dissociation into nitrogen and oxygen is prevented. NO concentrations of up to 5000 mg/m^3 (2650 ppm) could be measured in automobile exhaust gases [Leithe, 1]. The environmental significance of NO lies chiefly in its high reactivity, expecially its readiness to form nitrogen dioxide in the presence of atmospheric oxygen and/or ozone: $2\ NO + O_2 = 2\ NO_2$ + heat. With the NO concentrations available in the free atmosphere, this process is very slow, so that NO and NO_2 can exist side by side. It is impossible, however, to give a ratio representing the 24-hour day relationship of the two compounds, since NO parallels the traffic conditions during the day fairly closely, while NO_2 remains comparatively stable [Lies, 2].

Nitrogen dioxide (NO_2) is a brownish-reddish gas with a piercing smell, practically insoluble in water. A small amount of NO — the primary nitrogen oxidation product of the piston engine — oxidizes during dilution in the exhaust system; by far the greater proportion, however, does so during photochemical processes under the influence of sunlight with hydrocarbons in the atmosphere [Brockhaus, 3]. It was shown experimentally that, under conditions of concentrations above 100 mg/m^3 (53 ppm), 40% relative humidity, and at room temperature, this oxidation is rapid and practically complete.

Due to the two NO molecules involved, the reaction rate decreases as the square of the concentration: this explains the slow rate of oxidation, mentioned above, at atmospheric NO concentrations. The presence of atmospheric catalysts (e.g., hydrocarbons), however, could appreciably shorten the half-time value.

NO_2, in its turn, exists in equilibrium with its polymer dinitrogen tetroxide (N_2O_4). Below -9° C, the NO_2-N_2O_4 mixture is a colorless liquid consisting of nearly pure N_2O_4; at above 135° C, a blackish-brown gas consisting of nearly pure NO_2 occurs. At body temperature (37.5° C), the NO_2/N_2O_4 ratio is approximately 30 : 70; it is in this proportion that they also affect the body [Flury & Zernik, 4]. N_2O_4 reacts with water by forming nitrous and nitric acid, according to the formula $N_2O_4 + H_2O = HNO_3 + HNO_2$. NO_2 also reacts with water by forming nitric acid and nitrogen oxide, according to the formula $3\ NO_2 + H_2O = 2\ HNO_3 + NO$. It is not clear to what degree these reactions are responsible for the toxic effects.

6.2.2. General effects

6.2.2.1. Nitrogen oxide

In vitro, NO combines with hemoglobin to form nitrous hemoglobin (NOHb) which in vivo, however, immediately combines with the oxygen in the blood to form meta-hemoglobin (MEHb). It has, therefore, been impossible to demonstrate nitrous hemoglobin after inhalation of NO in the living animal, even with the most sensitive methods.

In contrast to normal hemoglobin, metahemoglobin can not form a reversible bond with oxygen. In man, the biological "base level" of metahemoglobin in the blood lies between 1 - 2% (0.15 - 0.30 g MEHb/100 ml blood). Higher values affect the oxygen capacity of the blood proportionately, interfering with the oxygen supply to the tissues. In general, MEHb values between 10 and 15% produce the first visible symptoms, i.e., a slight cyanosis. Toxic symptoms are obvious at MEHb values above 30%; more than 60% MEHb is lethal.

Experimentation with NO is difficult, due to the rapid conversion into NO_2 at higher concentrations.

6.2.2.2. Nitrogen dioxide

Together with sulfur dioxide, phosgene, and several "oxidants" (especially ozone), NO_2 is counted among the irritants affecting primarily the respiratory passages. Due to many years of industrial toxicological experience, as well as extensive animal experimentation, its effects are well known. The evidence of industrial medical research for the toxicological significance of NO_2 per se, however, is limited, since in such work areas we are dealing mostly with mixtures of NO and NO_2 or N_2O_4, and it is difficult to attribute any observed effects to any one substance in particular.

Depending on concentration and length and method of exposure, the following six crude degrees of intoxication can be distinguished [Air Quality Criteria for Nitrogen Oxides, 5]:

1) Acute exposure of 940 mg/m^3 (500 ppm) or more causes acute lung edema with death following within 24 hours. Death is due to the edematous effects on the alveolar gas exchange and the circulation, and the resulting oxygen deficiency in the tissues. In addition, the oxygen supply is impaired by nitrite formation on the part of NO_2, which can convert hemoglobin to metahemoglobin — a material incapable of carrying oxygen.

2) Acute exposure to 564 - 725 mg/m^3 (300 - 400 ppm) leads to pulmonary edema with broncho-pneumonia; death occurs 2 - 10 days after exposure.

3) Acute exposure to approximately 376 mg/m^3 (200 ppm) produces fibrous-obliterative bronchiolitis, leading to death within 3 - 5 weeks. This is the typical syndrome of the so-called "silo-loaders" disease [Lowry & Schumann, 6].

4) Acute exposure to between 94 - 188 mg/m^3 (50 - 100 ppm) produces a bronchiolitis lasting from 6 - 8 weeks, with focal interstitial pneumonia. Spontaneous remission is the rule.

5) Exposures to 47 - 141 mg/m^3 (25 - 75 ppm) generally cause bronchitis and broncho-pneumonias of various degrees. Recovery is complete if further exposures are avoided.

6) Long-term intermittent exposures of 18.8 - 75.2 mg/m^3 (10 - 40 ppm), common in certain work areas, can produce pulmonary fibrosis and emphysema [Vigliani & Zurlo, 7].

6.2.3. Effects of nitrogen monoxide (NO) on man and animal

6.2.3.1. Results in man

NO in concentrations common in the atmosphere is scarcely toxic. Exposures of 9.4 mg/m^3 and 0.62 mg/m^3 (5 ppm and 0.33 ppm) were used on 7 volunteers, and the absorption measured. With normal respiration, 80 - 90% of the NO was retained in the respiratory passages; with maximal respiration, more than 90% was retained [Wagner, 8]. No significant increase in metahemoglobin beyond the biological base level is likely at atmospheric concentrations.

The environmental importance of NO is due to its oxidation to the considerably more toxic NO_2. Any considerations of parameters for nitrogen oxides, therefore, are based on NO_2.

6.2.3.2. Animal experiments

The literature contains no systematic investigations on acute and chronic effects. Higher concentrations produced all stages and accompanying symptoms of oxygen deprivation, leading to chronic convulsions and death. Mice will collapse on their sides after 5 minutes at 6 g/m^3 (3200 ppm), and die after 7 minutes; at 3 g/m^3 (1600 ppm), collapse occurs after 7 minutes and death — after approximately 12 minutes. If exposure is terminated before death, at approximately 7 minutes, the animals recover after a few hours without after effects [Flury & Zernik, 4].

Guinea pigs showed no respiratory symptoms when exposed for 4 hours to concentrations from 19.7 - 94 mg/m^3 (16 - 50 ppm) [Murphy et al., 9]. Rats, gassed 24 hrs/day for 9 days with NO concentrations of 18.8 mg/m^3 (10 ppm), showed neither nitrous hemoglobin nor NO-metahemoglobin in their blood; no subsequent metahemoglobin determinations were made. The sensitivity of the method used was 0.1% NOHb or NOMEHb [Sancier et al., 10].

6.2.4. Effects of nitrogen dioxide (NO_2) on man and experimental animal

6.2.4.1. Results in man

Present-day industrial-toxocological findings are contradictory. According to Patty [11], no symptoms of illness appeared in workers exposed up to 6 - 8 hrs/day for 18 months to 9.4 - 56.6 mg/m^3 NO_2 (5-30 ppm) [average 16.8 - 37 mg/m^3 (10 - 20 ppm)]. According to Vigliani and Zurlo [7], even years of exposure to daily average concentrations of 56.6 - 66 mg/NO_2/m^3 in nitric acid plants are tolerated without any symptoms of difficulties whatsoever. Even the heightened susceptibility to inflammations of the respiratory passages after years of inhaling small quantities of nitrous gases is denied by various authors [Collen et al., 12; Baetjer, 13]. In contrast to these finding, Vigdortschik et al. [14] recorded the following symptoms [after 3 - 5 years of exposure to 4.7 mg/NO_2/m^3 (2.5 ppm)], which they attributed to chronic nitric oxide poisoning: pulmonary emphysema, chronic bronchitis, and inflammation of the oral mucosa. More precise data on diagnositc criteria are missing.

These contradictions are not easily resolved. In part, they are due to the fact that in a work area, NO_2 is present in varying amounts as one of many components of nitrous gases. Differences in exposure cycles also may play a role.

In spite of these limitations and contradictions, present day opinion holds that a long-term intermittent inhalation of 18.8 - 75.2 mg/NO_2/m^3 (10 - 40 ppm) can produce chronic pulmonary fibrosis and emphysema [5].

Rokaw et al. [15] repeatedly exposed healthy individuals, as well as some with diseases of the respiratory passages, for 2 - 3 hours at a time to NO_2 concentrations ranging from 0.94 - 5.6 mg/m^3 (0.50 - 3 ppm). They were unable to observe any NO_2-caused effects on constriction of the airways, breath frequency, or pulse frequency. In contrast, v. Nieding et al. [16, 17], as well as v. Nieding and Krekeler [18], using 2.8 and 9 mg/m^3 NO_2 (1.5 and 5 ppm) observed impairment of respiratory function and gas exchange in healthy individuals, as well as in bronchial patients. Forty to eighty individuals participated in the separate experiments, inhaling from a gate-valve for 15 minutes at a time, NO_2 air mixtures from 1.88 - 9.4 mg/m^3 (1 - 5 ppm). Various respiratory and circulatory functions were measured prior to the experiment, 10 minutes after its beginning, and 10 minutes after NO_2 inhalation had stopped: respiratory frequency, breath volume/minute, oxygen intake, and alveolar and arterial O_2 or CO_2 pressure. Moreover, in chronic bronchitis patients, the resistance of the airways was measured plethysmographically prior to and after 30 inhalations of NO_2.

In chronic bronchitis patients, significant NO_2-related dysfunctions in airway resistance appeared after 30 inhalations (approximately 90 seconds) from 3 mg/m^3 (1.6 ppm) on; the arterial partial O_2 pressure was affected after 10-minute inhalation of NO_2 at 7.5 mg/m^3 (4 ppm). Complete reversibility of the impairment could be proven for partial O_2 pressure after the exposure was terminated. This study supplied no data for restricted peripheral circulation; others, however, showed that for this measurement, the maximum effect was not registered until 30 minutes after the end of exposure (10 minutes to 2.5 - 4 ppm NO_2) [Abe, 19].

The mechanism by which NO_2 produces constriction of the airway is as yet unclear. V. Nieding and Krekeler [18] suggest that histamine is released by the mast cells in the bronchii, causing edema of the bronchial mucosa; this could be the basic cause for the observed effects. When an antihistamine was administered, 9.4 mg/m^3 (5 ppm) of NO_2 for 30 inhalations revealed no impairment of the circulation; antilinergic or sympatomimetic drugs had no such effect. In this connection, we might refer to the animal experiments of Thomas et al. [20]; after 4 hour exposures to 0.94 mg/m^3 (0.5 ppm), they were able to observe degranulation of bronchial mast cells containing histamine and heparin, as well as of those in the pleura and mediastinum. The release of histamine certainly plays a causative role in acute NO_2 effects.

The investigations of v. Nieding et al. also permit certain conclusions concerning the differences in airway constriction for healthy individuals and those with prior bronchial impairment. Basically, both groups evinced similar changes in pulmonary functions under NO_2 stress. For the well, as well as for the ill, the absolute drop (NO_2-caused) of arterial O_2 pressure is approximately the same. In healthy individuals, however, the initial pressure is approximately 93 torr [v. Nieding et al., 16a] — considerably higher than in chronic bronchitis patients with 76 torr; in the healthy, NO_2 causes only a 1% drop in O_2 saturation, but approximately 2% for the ill — who, therefore, suffer a greater loss in the O_2 supply to the tissues when exposed to NO_2 concentrations upwards from 7.5 mg/m^3 (4 ppm).

6.2.4.2. Odor perception and impairment of well-being

For rapidly increasing concentrations, the odor threshold for NO_2 is consistently found to be below 0.94 mg/m^3 (0.5 ppm) [Shalamberidze, 21; Henschler et al., 22; Rumsey and Cesta, 23]. Shalamberidze [23] found the threshold to be 0.225 mg/m^3 (0.12 ppm) for especially sensitive individuals; Henschler et al. [22] found that 33% of the subjects detected odor at 0.225 mg/m^3 (0.12 ppm), 61% — 0.415 mg/m^3 (0.22 ppm), and 100% — at 0.835 mg/m^3 (0.42 ppm). A statistical analysis of these data [Finney, 24] gave the 50% threshold at 0.314 mg/m^3 (0.167 ppm), with 95% reliability at 0.171 mg/m^3 (0.09 ppm) to 0.426 mg/m^3 (0.227 ppm). According to the data of Henschler et al.[22], the recognition and identification threshold [Fodor and Winneke, 25] lies between 0.41 mg/m^3 (0.22 ppm) and 0.79 mg/m^3 (0.42 ppm). Rumsey and Cesta [23] limit themselves to the statement that the perceptual threshold was found to be below 0.94 mg/m^3 (0.5 ppm).

The results reported by Henschler et al. [22] also permit some statements concerning the habituation to NO_2-caused odor and irritant effects. With large individual differences, odor perception disappeared after about 5 - 10 minutes exposure to the threshold concentration (0.167 ppm); 90 seconds after the stimulus was withdrawn, however, it returned. Irritation of the upper respiratory tract due to repeated exposure showed a similar adaptation. At the initial NO_2 exposure, the volunteers reported irritation, dryness and roughness of the throat up to a slight "choking" sensation, although no correlation could be established between concentration and intensity, or frequency of symptoms. In the following experiments, irritability was greatly reduced — to such a degree that after several exposures, even 38 mg/m^3 NO_2 (20 ppm) was tolerated for more than 30 minutes with scarcely any difficulty. At 57 mg/m^3 NO_2 (30 ppm), however, distinct signs of irritation were registered, which increased with exposure time and was not subject to adaptation, i.e., prickling of the nasal and pharyngeal mucosa (after 30 - 40 minutes), changing to a burning sensation after 70 minutes. At this stage, the first coughing responses also appeared. During further exposure the burning sensation travelled down the air passage, was finally felt deep in the chest, and was accompanied by considerable mucus secretion and shortness of breath. After an exposure of 2 hours, this condition was felt to be definitely troublesome; the feeling of pressure and mucus secretion lasted several hours beyond the experiment.

Pronounced adaptation was seen when exposures were increased gradually. When NO_2 concentrations were increased from zero to 47 mg/m^3 (25 ppm) over a 50 minute period, odor perception was practically nonexistent; irritation of the air passages also was greatly decreased [Henschler et al., 22].

6.2.4.3. Epidemiological results

Large scale epidemiological studies on school children were carried out in the vicinity of a large TNT factory [Shy et al., 26a, b; Pearlman et al., 27]. The forced expiratory volume

$SK_{0.75}$[*] was used as the objective measurement of respiratory function. The families of the children were also surveyed systematically as to frequency of respiratory illnesses.

School children and their families in variously polluted residental areas were tested. The authors distinguish one area with relatively high NO_2 - NO_3 pollution (referred to subsequently as the NO_2-NO_3 area), one area with high dust pollution (dust area), and two control areas with comparatively low pollution. Three schools were encompassed in the NO_2-NO_3 area, two — in the control area, and one — in the dust area. A testing station was set up in each school. Table 1 shows the concentrations of several gaseous and particulate pollutants over a 6-month period (November-April). SO_2 measurements were also made, but were discontinued after 1 month, since the average values over 24 hours remained below 0.0038 mg/m^3 (0.015 ppm). The Jacobs-Hochheisser method [Jacobs and Hochheisser, 30] was used for NO_2 measurements. Table 1 shows that the maximum NO_2 values in the NO_2-NO_3 area are twice as high as those in the control area, and the NO_3 values — three times as high. Values obtained at School 3 matched those of the control areas. Since this school was only 2 km in the predominant wind direction from the TNT factory, the control areas, however, approximately 10 km, the authors attributed the surprisingly lower values to peculiarities of the location, or to errors in measurements.

In terms of socio-economic and demographic indices (father's education, market value of residence, number of persons per bedroom), the NO_2-NO_3 area and the control areas were perfectly comparable; only the dust area appeared deprived socio-economically

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[*] The English abbreviation $FEV_{0.75}$ (forced expiratory volume) represents the maximum exhaled air volume exhaled in .75 sec (in liters) after maximum inhalation. The German Tiffeneau-Test value (expelled breath test), however, represents the volume expelled within 1 second.

TABLE 1. AVERAGE VALUES, 90% VALUES, AND SCATTER OF VARIOUS GASEOUS AND PARTICULATE AIR POLLUTANTS IN THE TESTING AREAS (from Shy et al., [26a])

	NO_2-NO_3 area school 1	2	3	Dust-area school	Control school 1	2
NO_2 (ppm) Average 90th percentile Scatter	0.109 0.242 0.098	0.078 0.141 0.054	0.062 0.098 0.040	0.055 0.087 0.024	0.063 0.096 0.030	0.043 0.069 0.021
NO_3-particulate ($\mu g/m^3$)	7.2 14.8 9.1	6.3 13.4 5.8	3.8 8.0 4.6	2.4 4.6 1.7	2.6 5.9 2.6	1.6 3.1 1.0
Sulfur-containing particulate matter ($\mu g/m^3$)	13.2 22.6 6.8	11.4 19.2 6.4	10.00 19.5 4.9	10.7 17.3 4.6	9.8 15.8 4.5	10.0 15.6 4.5
Total particulate matter ($\mu g/m^3$)	96 183 63	83 138 46	63 108 42	99 181 58	72 128 45	62 112 35
Soiling index*	0.80 1.46 0.51	0.89 1.73 0.64	0.91 1.84 0.68	1.09 4.37 1.67	1.39 3.29 1.20	1.23 2.53 0.89

* The soiling index quantified, by extinction measurements, the degree of blackening of a filter through which air was suctioned for four hours.

compared to the others. Smoking habits in individual households of the separate areas also were comparable; approximately 60% had at least one cigarette smoker.

Nine hundred eighty-seven second-graders participated in the pulmonary function tests thouughout the 4 testing areas. Since the $SK_{0.75}$ corresponds linearly to body size, all measurements were corrected accordingly. Table 2 shows the variance analysis of the significance tests:

TABLE 2. VARIANCE ANALYSIS OF THE EFFECTS OF THE FACTORS "GENDER", "TEST MONTH" AND "TEST AREA" ON $SK_{0.75}$ PERFORMANCE IN LITERS (from Shy et al. [26a])

Variance-source (factor)	Mean square	F value	Exceeds probability (significance)
Gender (male vs. female)	0.3852	189.3	$p < 0.01$
Test month (November vs. March)	0.0318	15.6	$p < 0.01$
Test area			
NO_2-NO_3 vs. control areas 1 and 2	0.0098	4.8	$p < 0.05$
Dust area vs. control areas 1 and 2	0.0011	0.6	Not significant
Control area 1 vs. control area 2	0.0004	0.2	Not significant

Although the factor "test area" appears low compared to the other two factors, and the performance values do not show large differences between the test areas, the measurements obtained in the NO_2-NO_3 areas are significantly ($p < 0.05$) lower than those from the control areas [Shy et al., 26a].

Even clearer differences could be shown between the test areas in response to inquiries about nonspecific respiratory illnesses [Shy et al., 26b]. Data were obtained from post-cards which had to be mailed every other week by the 968 families of the school children who had volunteered; these had to report if anyone in the family had been subject to colds or sore throats within the past 14 days. Details were followed up by telephone calls (identity, age and sex of patient, seriousness and course of the illness).

Table 3 shows the relative excess* of respiratory illness in the exposure area during 24 test weeks, broken down into family segments.

TABLE 3. RELATIVE EXCESS* IN RESPIRATORY ILLNESS OF VARIOUS FAMILY SEGMENTS. COMPARISON OF EXPOSURE AREAS TO CONTROL AREAS (from Shy et al. [26b])

Family segment	NO_2- NO_3 area	Dust area	Control area
Whole family	+ 18.8	+10.4	0
Second grader	+ 16.8	+12.6	0
Siblings	+ 16.0	-0.06	0
Mother	+ 18.3	+34.2	0
Father	+ 31.5	+22.8	0

By subjecting the frequencies of respiratory illness in the various living areas to the Chi^2 Test for the experimental exposures, we revealed significant differences between the NO_2-NO_3 area and the control areas (Table 4).

TABLE 4. CHI^2 TEST FOR SIGNIFICANT DIFFERENCES IN INCIDENCE OF RESPIRATORY ILLNESSES IN TEST AREAS VS. CONTROL AREAS (from Shy et al. [26b])

Family segment	NO_2-NO_3 area vs. control	Dust area vs. control
Second graders	$p < 0.01$	Not significant
Siblings	$p < 0.02$	Not significant
Mothers	$p < 0.001$	$p < 0.05$
Fathers	$p < 0.02$	$p < 0.01$

$*\left(\frac{\text{Illnesses in exposed group}}{\text{Illnesses in control group}} - 1\right) \times 100.$

An increase of respiratory illnesses in the NO_2-NO_3 area can, therefore, be considered statistically significant.

A replication study of the same [Pearlman et al., 27] data largely confirmed the findings of Shy et al. [26 a,b]. These authors emphasized illnesses of the lower air passage (bronchitis, pneumonias). In order to test the effects of dosages, they distinguished three living areas in terms of basic NO_2-NO_3 stress: a low-stress area (NO_2-:0.043 ppm NO_2; 1.6 μg NO_3/m^3), corresponding to control area 2 (according to [26a]); a medium stress area (NO ± 0.063 ppm NO_2; 2.6 μg/NO_3/m^3), i.e., corresponding to control area 1 (according to [26a]), and a high stress area (NO_2 +: 0.084 ppm NO_2; 5.8 μg NO_3/m^3, i.e., matching the three test areas (omitting the dust area of [26a]).

Questionnaires were sent to the parents of more than 1700 first and second graders and more than 1100 preschoolers in these three test areas. The parents were asked to recall the type and frequency of lower respiratory tract illness their children had suffered within the last three years (mid-1966 to mid-1969). Their replies were checked against medical records and found to be 70% reliable.

The differences in nitrogen oxide exposure did not seem to affect the frequency of pneumonias in the three test areas; bronchitis, however, was more common in the more heavily polluted NO ± and NO + areas (Table 5).

A monotonic dosage effect is present primarily for the children exposed for a three-year period. According to this, 0.118 NO_2/m^3 (0.063 ppm) in conjunction with 0.0026 mg NO_3/m^3 seems to constitute a stress threshold beyond which a bronchitis attack becomes more probable for children between 4 - 7 years of age after an exposure period of 2 - 3 years.

TABLE 5. NUMBER OF CHILDREN (IN %) WHO HAD AT LEAST ONE BRONCHITIS ATTACK DURING THE EXPOSURE PERIOD (from Pearlman et al. [27])

Living area with NO_2-stress	Exposure length of pupils (years)			Exposure length of children (years)		
	1	2	3	1	2	3
NO_2+ 0.156 mg/m^3 (0.083 ppm)	20.9%	34.7%*	32.2%*	33.3%	37.3%	46.8%*
NO_2± 0.118 mg/m^3 (0.063 ppm)	31.6%	45.5%*	31,2%*	26.2%	29.5%	50.5%*
NO_2- 0.081 mg/m^3 (0.043 ppm)	25.1%	20.3%	23.2%	21.1%	34.0%	36.3%

*Significant deviation of NO_2.

6.2.4.4. Animal experiments

Short-term exposures

In experiments on rats, it was shown that the product concentration × time (c × t) does not constitute a constant for NO_2; on the contrary, as concentration decreases, progressively longer exposure times are required to kill 50% of the exposed animals. Short exposure times combined with high NO_2 concentrations, therefore, are more toxic than comparable long-term exposures (cf.,Table 6).

For 24-hour exposures, 76 mg NO_2/m^3 (40 ppm) constitutes the LC_{50} for rats [Ross and Henschler, 30]; death is always due to pulmonary edema [Gray et al., 29].

The lethality of acute NO_2 stress can be attenuated by previous sublethal NO_2 exposures [Henschler, 31; Stokinger, 32].

TABLE 6. MORTALITY (LC_{50}) OF RATS AS A FUNCTION OF NO_2 CONCENTRATION AND LENGTH OF EXPOSURE [GRAY ET AL. [29]

Exposure (minutes)	Concentration mg/m^3	 ppm	c x t ppm x min.
2	2715	1445	2890
5	1560	833	4165
15	790	420	6300
30	325	174	5220
60	315	168	10080
240	165	88	21120

In a systematic series of experiments, Henschler et al. [33a, b] investigated the conditions and mechanism of this heightened resistance in mice. When mice were exposed for six hours to sublethal NO_2 concentrations from 4.7 mg/m^3 to 116 mg/m^3 (2.5 - 61.8 ppm) and, four days later, to a lethal concentration of approximately 1230 mg/m^3 (650 ppm) for 30 minutes, survival time increased linearly with the logarithm of the pretreatment sublethal concentration. Even a pretreatment with only 4.7 mg/m^3 (2.5 ppm) NO_2 increases the survival time by 59% ($p = 0.05$) over that of control animals without pretreatment.

The same result, although to a lesser degree, can be shown when the extent of edema (decrease in pulmonary fluid content) is used as a criterion for the protective effect. This becomes significant only with pretreatment concentrations of 9.5 mg/m^3 (5 ppm). The extent of protection of a one-time sublethal NO_2 treatment depends on the time elapsed before the subsequent lethal treatment: it reaches a maximum between the second and fifth day and then decreases; even 10 - 40 days later, however, it can still be demonstrated in comparison with control animals.

Histological examination showed that the protection of sublethal NO_2 stress against subsequent exposures to NO_2 is due to a pathological, inflammatory response of pulmonary tissue. Based on light-microscope evidence, Henschler et al. [33b] attributed the protective effect to a highly localized edema in the interstices of the alveolar septa, which increased the diffusion path between the inner wall of the avleoli and the capillaries. This impairment in diffusion inhibits the penetration of the poison, but does not — or only insignificantly so — impair the respiratory gas exchange. More recent electron-microscope findings, however, did not corroborate the existence of an interstitial edema in mice after 6-hour exposure to NO_2 66.1 mg/m^3 (35 ppm) [Dillman et al., 34]. However, the cellular elements between the alveoli and the capillaries increased in volume, so that the mechanistic interpretation of resistance as due to diffusion-impairment may still be valid.

Other investigators were able to demonstrate structural changes in lung tissue even after acute exposures to much lower NO_2 concentrations. Buell et al. [35] exposed 3 rabbits for one hour each to 1.9 mg/m^3 or 9.4 mg/m^3 (1 or 5 ppm). An unexposed animal served as control. Two animals were killed immediately after exposure, the third one — 24 hours later. Lung tissue slides were prepared. UV-spectrophotometric analyses showed that the structural proteins collagen and elastin can be reversibly changed in the exposed animals. The authors suggest that the acidified inner environment (due to NO_2) may interfere with the metabolism of pulmonary tissue, and that the repeated structural changes of the proteins may contribute to the formation of pulmonary edemas.

Thomas et al. [20] exposed rats for one hour to 1.89 mg NO_2/m^3 (1 ppm), or for 4 hours to 0.94 mg/m^3 (0.5 ppm). The mast cells in the bronchi, the pleura, and the mediastinum were examined. The mast cells are polymorphonuclear, basophile granulocytes, which normally constitute 0.5% of the leucocytes. Degranulation and cell breakdown could be observed after both exposure tests. Below an exposure of 0.5 ppm, this was especially true in the mediastinal region. These morphological changes were shown to be completely reversible in several animals that were killed only after 27 hours had elapsed since the 1-hour 1.9 mg/m^3 exposure. The biological significance of these findings is not clear. It is known, however, that mast cells are especially numerous in healed-over, previously-chronically-inflamed tissue sections, and that the heparin found in mast cells plays a role in the formation of collagen fibers; the authors reason, therefore, that long-term exposure to less than 0.94 mg/m^3 may favor inflammatory processes in the lungs.

Guinea pigs, exposed to short term inhalations (2 - 4 hours) of 9.8 - 24.4 mg NO_2/m^3 (5.2 - 13 ppm), developed an increase in respiratory rate, but a decrease in inhaled breath volume [Murphy et al., 9]. At 24.4 mg/m^3, the frequency after 60 minutes of exposure was approximately 80% above the initial value, which was regained only 4 hours after the end of exposure. At 9.8 mg/m^3, the frequency increase for a 4-hour exposure amounted to maximally 20% of that after 380 minutes of exposure. At 24.4 mg/m^3, the breath volume decreased to maximally 50% of the initial volume after approximately 100 minutes; at 9.8 mg/m^3 — maximally 20% after approximately 240 minutes of exposure. Similar results were obtained with squirrel monkeys [Henry et al., 36]. Between 18.8 and 28.2 mg NO_2/m^3 (10 - 15 ppm) exposure of 2 hours, the frequency remained the same, but total breath volume and inhalation per minute volume decreased. The breathing frequency rose only at 65.8 and 94 mg/m^3 (35 and 50 ppm), and beyond.

Long-term exposure

Ross and Henschler [30], as well as Henschler and Ross [37], report several experiments in which three groups of mice were exposed to various exposure cycles of 76 mg NO_2/m^3 (40 ppm) for

15 months. Since this concentration corresponds approximately to the LC_{50} at 24 hours, the animals were acclimatized prior to the experiment by means of a one-time half-day pretreatment at 38 mg/m^3 (20 ppm). Group A was exposed twice for 48 hours per week; group B — once for 48 hours every ten days; and group C — once for 48 hours every 30 days. All three groups showed similar cellular proliferation at the alveolar septa, always at the branch points of the bronchi, and always at the point of transition between bronchiolus and alveolar passage. Similar proliferation of cells has been observed in man after acute effects of nitrous gas exposure [Probst, 38].

The groups showed considerable qualitative differences in the extent of these effects. Group A (2-day exposure-free interval between 2-day-long exposures) quickly developed a steady proliferation state, whose severity was considerably less than in the reaction to one-time acute exposure. Exposure-free intervals of 10 days (Group B) and, even more clearly, of 30 days (Group C) resulted in pronounced mitotic activity with many abnormal cell divisions,as well as giant cells at each exposure. Every repetition increased these phenomena [Ross and Henschler, 30]. These differences in the pulmonary parenchyma response, as correlated to the exposure cycle, were also evident in the overall condition (weight measurements) of the animals [Henschler and Ross, 37]. Intermittent NO_2-exposures, with only 2-day exposure-free intervals, thus seem to convey protection, whereas an increase in the exposure-free interval seems to decrease the protective effect. It is unclear whether this protective effect is due to the same mechanism as that observed in edema inhibition after acute NO_2 pretreatment [Henschler et al., 33b].

Corresponding to the results obtained with one-hour exposures, Buell et al. [35], using intermittent long-term exposures (4 hours/day, 6 days) on rabbits, could demonstrate structural changes in structural proteins — particularly collagen fibers in lung tissue — at concentrations as low as 0.47 mg NO_2/m^3 (0.25 ppm). These changes were only partially reversible, and could be found even 7 days after the end of exposure.

Emphysemous or similar lung tissue changes due to NO_2 exposure were reported by several authors [Blair et al., 30; Freeman and Haydon, 40; Haydon et al., 41; Freeman and Furiosi, 42]. Blair et al. [39] exposed mice for 1 - 12 months daily for 6, 18, or 24 hours to only 0.94 mg NO_2/m^3 (0.5 ppm). Histopathological findings after 3, 6, and 12 months — broken down according to 6 or 24 hours exposure per day — are summarized in Table 7. Under all experimental conditions, the alveoli were distinctly enlarged compared to those of control animals, most clearly so after 12 months of NO_2 exposure. The histopathological symptoms (inflammation of the bronchioli respiratorii, erosion of the epithelial surface, as well as blockage of the bronchioli-alveoli passage) matches — according to the authors — that of focal emphysema in the early stages of development.

Gray et al. [43] obtained similar results in rats using 16.9 or 26.4 mg NO_2/m^3 (9 or 14 ppm). After 6 weeks of exposure, they found inflammatory reactions in the respiratory tract in the form of rhinitis, tracheitis, and interstitial pneumonia.

After more than 8 weeks of exposure, the inflammation had died down; circumscribed regions of emphysema had formed. Other investigations [Freeman and Haydon, 40; Haydon et al., 41], by exposing rats to 47 mg NO_2/m^3 (25 ppm) for 20 weeks and to 23.8 mg/m^3 (12.5 ppm) for 30 weeks, also obtained clearly pathological changes in lung tissue. The weight of the lungs was more than twice that of the controls; the passages between the terminal bronchi and the alveoli were constricted by cell fragments and accumulated macrophages, and the cilia covered by mucus. Using 7.5 mg/m3 (4 ppm) for 16 weeks resulted in constrictions of the bronchio-alveolar duct; but even 3.76 mg NO_2/m^3 (2 ppm), used continuously throughout the lifetime of the animal resulted in pathological changes of the bronchial epithelium, particularly the loss of cilia and epithelial cells enlarged by 30%, which were visible on electron-micrographs.

TABLE 7. PULMONARY CHANGES IN MICE UNDER VARIOUS MONTHS' EXPOSURE TO 0.94 mg NO_2/m^3 (0.5 ppm) (From Blair et al. [39], modified according to Air Quality Criteria for Nitrogen Oxides [5])

Total exposure time	6 hrs/day	24 hrs/day
3 months	Interstitial pneumonia, characterized by interstitial & peribronchial infiltration by lymphocytes. Bronchial epithelium unchanged. Alveoli partially enlarged. Bronchioli clear. Alveolar septa partially broken	Several bronchioli plugged by acidophile cells; epithelium is cylindrical at those sites; cilia absent. Alveoli distal to plugged portions distended, their walls thinner. Alveolar septa partially broken.
6 months	Interstitial pneumonia as above. Bronchial mucosa clearly inflamed. Erosion of surface, loss of cilia. Bronchioli-alveoli transition completely blocked; in some regions, with cell fragments. Bronchial epithelium unchanged. Alveoli somewhat enlarged (as above). Some septa broken (as above).	Increased interstitial pneumonia. Bronchial epithelium partially covered with cylindrical cells and mucus. Alveoli enlarged; some septa broken.
9 months	Interstitial pneumonia clearly attenuated (compared to 3 & 6 months). Alveoli less enlarged than for 3 and 6 months.	Same as for 6 months

(Table continued on following page)

TABLE 7. (continued)

Total exposure time	6 hrs/day	24 hrs/day
12 months	Moderate interstitial pneumonia. Slight erosion of bronchial epithelium.	Severe interstitial pneumonia with pronounced interstitial and peribronchial lymphocyte infiltration. Several lung lobes in a stage of grey hepatisation with exudate in alveoli and infiltration of polymorphonuclear leucocytes. Slight erosion of bronchial epithelium.

The same life-long exposure at 1.5 mg/m^3 (0.8 ppm) caused qualitatively similar, although less pronounced, effects which were regarded as early stages of emphysema [Freeman and Furiosi, 42]. In contrast, however, Wagnet et al. [44], by exposing dogs, rabbits, guinea pigs, rats and mice to 1.9, 9.4, and 47 mg/m^3 (1, 5, and 25 ppm) for 10 - 18 weeks (6 hrs/day; 5 days/week), could not detect any histopathological changes in lung tissue due to NO_2. They made histological findings and frequently found symptoms of a diffuse interstitial pneumonia, often in conjunction with chronic bronchiolitis, but the same symptoms could be observed just as frequently in the control animals.

The NO_2-caused loss of resistance to bacterial pneumonia was shown to be an especially sensitive criterion [Purvis and Ehrlich, 45; Ehrlich, 46; 47; Ehrlich and Henry, 48; Henry et al, 49].

When albino mice were exposed from 7 days to 12 months intermittently (6 or 18 hours per day) or continuously (24 hours per day), to only 0.94 mg NO_2/m^3 (0.5 ppm), and then infected with Klebsiella pnumoniae, their mortality rate after three months increased considerably over that of the equally infected, but unexposed, control animals (Table 8).

The animals exposed for 3 and 6 months show a distinct mortality maximum. Whether the striking relative decrease in mortality after 9 or 12 months of exposure — not discussed by the authors — is truly significant, as possibly due to an increase in tolerance, must remain open to question. To be sure, the attenuated reaction of the pulmonary parenchyma to NO_2 observed by Blair et al. [39] after 9 months exposure compared with 3 and 6 months (cf., Table 7) would certainly correspond to such an interpretation. Intermittent exposures (0.5 ppm; 6 or 18 hrs/day) resulted in a much less pronounced NO_2-caused mortality increase over nonexposed, but equally infected controls, which became significant only after 6 months. According to this criterion, then, chronic NO_2 exposure seems to be much more damaging than intermittent exposure.

TABLE 8. MORTALITY OF NO_2 EXPOSED MICE AND NONEXPOSED CONTROLS INFECTED WITH BACTERIA (K. pneumoniae) (from Ehrlich and Henry, [48])

Exposure time (continuous 24 hr/day)	Mortality of infected controls (%)	Mortality of infected and exposed animals (%)	Chi^2	Significance
7 Days	66,7	67,5	1,5	Not sign.
14 Days	45,4	51,1	1,5	Not sign.
1 Month	40,8	45,8	1,5	Not sign.
2 Months	68,0	78,0	1,67	Not sign.
3 Months	40,6	60,5	16,26	0,001
6 Months	46,3	70,0	13,23	0,001
9 Months	57,7	70,0	2,91	0,10
12 Months	63,3	86,7	4,36	0,05

Besides mortality, the capacity of the lung to rid itself of viable bacteria (clearance rate) is also negatively affected by NO_2. In control animals, 50% of the Kl. pneumoniae had been removed from the lung after approximately 1 hour; but in animals exposed to NO_2 intermittently or continuously for 12 months, the period required to clear 50% of the inoculum had nearly doubled, while after 6 months of exposure for 24 hours/day, this period had increased to 1.8 hours. Thus, the clearance rate of the lungs is also much more significantly affected medically by the 24 hours/day exposure than by intermittent exposure.

Henry et al. [49] tested mortality and lung clearance rate of squirrel monkeys, exposed chronically to NO_2 at 18.8 mg/m3

(10 ppm) for 1 month and 9.4 mg/m^3 (5 ppm) for 2 months (24 hrs/day), and then infected with Klebsiella pneumoniae. They also tested the effect of NO_2 on resistance to virus infection (influenza-A/PR.-8-virus)by exposing the animals to 18.8 mg/m^3 and 9.4 mg/m^3 (10 and 5 ppm) (continuous exposure), 24 hours after they had been infected. None of the bacterial controls died; but 25% of the animals previously exposed for 1 month to 10 ppm NO_2 died, as did 2 out of 7 animals pre-exposed for 2 months to 5 ppm. All the animals (6 out of 6) exposed to 10 ppm, 24 hours after viral infection, died; 1 out of 3 of those exposed to 5 ppm died; none of the controls which were infected with influenza virus without any subsequent NO_2 exposure died.

According to the authors, NO_2 weakens the defenses of the organism; bacteria and viruses can, therefore, reproduce, and heightened mortality results. They refer to the work of Weissbacker et al. [50], who showed that in vitro, NO_2 impairs the viability of alveolar macrophages; such NO_2-caused changes in phagocytosis activity makes a decrease in resistance to bacterial infection very likely. The rise in mortality after experimental infection with a virus may be associated with an NO_2-linked inhibition of interferon production. Alveolar macrophages of rabbits exposed to influenza virus were shown to have no resistance against subsequent infection with small pox virus when the animals had been exposed for 3 hours to 47 mg NO_2/m^3 (25 ppm) up to 24 hours prior to infection with influenza; such cells are not able to produce interferon [Valand et al., 51].

Drukey and Preussman [52] formulated the hypothesis that inhaled nitrogen oxides might react with tissue amines at the respiratory mucosa to form nitro-amines, which are known to be carcinogenic. Up to now, however, animal experimentation does not verify the resulting assumption that nitrogen oxides might have carcinogenic effects.

Wagner et al. [44] exposed mice with a hereditary high rate of spontaneous tumor formation to chronic-intermittent NO_2 dosages (9.4 mg/m^3, i.e., 5 ppm; 16 months, 5 days/week, 6 hrs/day) to test NO_2-linked increases in tumors after 12, 14, and 16 months. Table 9 shows the results:

TABLE 9. NUMBER OF MICE WITH LUNG TUMORS UNDER EXPOSURE AND CONTROL CONDITIONS, AFTER 12, 14, AND 16 MONTHS OF EXPOSURE (from Wagner et al., [44])

	NO_2	Control		
Exposure	Tumorous animals per group	Tumorous animals per group	Chi^2	Significance
12 months	7/10 = 70 %	4/10 = 40 %	1,82	$p > 0,10$
14 months	7/15 = 47 %	8/15 = 53 %	$<1,5$	$p > 0,10$
16 months	15/24 = 62 %	15/24 = 62 %	$<1,5$	$p > 0,10$

After 12 months exposure to NO_2 the number of animals with lung tumors rises slightly, but not significantly; with longer exposures, this slight rise of tumor formation rate gradually disappears again. In spite of this, the authors do not want to altogether exclude the possibility that NO_2 might possibly favor tumor formation.

Henschler and Ross [37] also report their opinion as to the carcinogenicity of NO_2. They base it on the histological findings of the above-mentioned exposure experiments on mice. Thre groups of mice were exposed intermittently (2 × 48 hrs/week; 1 × 48 hrs/10 days; 1 × 48 hrs/30 days) to 76 mg NO_2/m^3 (40 ppm) for 15 months. Lung tumors in these animals were exclusively benign adenomas, which are known to arise spontaneously in mice; carcinomas or neoplasmas were not found in a single animal. With increasing dosage, the adenoma rate decreased, and was, therefore, lowest in the 2 × 48 hrs/week group. In order to test the possible tumor-accelerating effect of chronic NO_2 exposure, NO_2-exposed animals were compared with non-exposed control animals; ordinary mice plus another group with a high spontaneous tumor rate were examined. The NO_2 animals were again exposed intermittently for 16 months (1 × 48 hrs/10 days) to 76 mg NO_2/m^3. Histological examination of the lungs after 16 months of exposure gave the results shown in Table 10.

TABLE 10. NUMBER OF ANIMALS WITH LUNG TUMORS, NORMAL AND TUMOR-SUSCEPTIBLE MOUSE VARIETIES, AFTER CHRONIC NO_2 EXPOSURE (16 MONTHS: 1 × 48 HRS/10 DAYS; 40 PPM) AND AFTER CONTROL EXPOSURE
(from Henschler and Ross [37])

	Variety without high tumor susceptibility		Tumor-susceptible variety	
	Tumorous animals/group	%	Tumorous animals/group	%
NO_2	21/37	57	15/20	75
Control	28/39	72	18/23	79
Chi^2	1,87		1	
Significance	Not significant		Not significant	

Accordingly, the tumor rate does not rise after 16 months of NO_2 stress. The same holds true for the number of tumors per animal (not shown in Table 10), which was also higher in the control mice than in the NO_2 mice.

The carcinogenicity of nitrogen oxides postulated by Druckrey and Preussmann [52] is, therefore, not proven by the presently available results of animal experimentation.

6.2.5. Summary and conclusions

It has already been pointed out that the environmental significance of nitrogen oxide (NO) is primarily due to its oxidation to nitrogen dioxide (NO_2), and that, therefore, any limiting values for nitrogen oxides must be based on NO_2. Corresponding to previously specified considerations, such limiting values should be constituted so as to exclude health damage or stress to the exposed population. The observations and results reported above have shown that not only the degree, but also the cycle, of exposure is significant for the toxic effects of NO_2. The most important results concerning the effects of low NO_2 concentrations on animals and man, together with the relevant data on exposures, are summarized in Table 11.

Obviously, results in humans — i.e., in the present case, epidemiological data — are of primary importance for the determination of limiting values. A critical review of the pertinent studies [Shy et al., 26a, b; Pearlman et al., 27] is therefore essential. It is well known that due to numerous hard-to-control factors, epidemiological investigations often cannot reveal clear-cut cause and effect relationships. It must be admitted that the studies under discussion here are not to be viewed as offering proofs in the strict experimental sense. For instance, it must be left open to question to what extent other, not-measured atmospheric impurities — e.g., ozone — might have contributed to the symptoms observed. Nor can we be certain that the measurements for gaseous and particulate concentrations are representative for the entire exposure term of the children, or whether the chronic sensitization of the air passages occurred at concentrations other than those measured. On the other hand, it can be seen that comparability of the total data as to socio-economic and demographic criteria, as well as to cigarette smoking in families, was tested and verified in an exemplary manner. It should also be pointed out that the epidemiological findings are corroborated qualitatively by the animal experiments on lowering of

TABLE 11. ACUTE AND CHRONIC EFFECTS OF LOW NO_2 CONCENTRATIONS (5 PPM) ON MAN AND ANIMAL (SUMMARY)

NO_2 concentration	Exposure length, mode	Species	Effect	Source
0.117-0.203 mg/m^3 (0.062-0.109 ppm) In addition: 0.005-0.009 mg/m^3 particulates containing NO_3	Chronic 1 - 2 yrs 24 hrs/day	Man	Significant decrease of capacity per sec in children (5-6 yrs) Significant increase of general respiratory illnesses in children and adults	[26a, b]
0.118-0.156 mg/m^3 (0.063-0.083 ppm) In addition: 0.003-0.006 mg/m^3 particulates containing NO_3	Chronic 1 - 3 yrs 24 hrs/day	Children (3 - 7 years)	Significant increase of acute bronchitis. Monotonic relation for dosage-effect relation (for 3 yr. exposure)	[27]
0.314 mg/m^3 (0.166 ppm)	-	Man	Odor perception (50% value). Reliability (95%): 0.171 - 0.426 mg/m^3 Adaptation after 5 - 10 minutes	[22]
1.47 mg/m^3 (0.25 ppm)	Chronic 6 days; 4 hr/day	Rabbit	Partially reversible changes in lung collagen; in part visible 7 days after termination of exposure	[35]
0.94 mg/m^3 (0.5 ppm)	Chronic 3-12 months 6-24 hrs/day	Mouse	Interstitial pneumonia and enlargement of the alveoli Interpretation: early stages of emphysema	[39]

(Table continued on following page)

TABLE 11. (continued)

NO_2 concentration	Exposure length, mode	Species	Effect	Source
0.94 mg/m^3 (0.5 ppm)	Acute 4 hours	Rat	Degranulation of mast cells in mediastinum Interpretation: slight inflammatory reaction	[20]
0.94 mg/m^3 (0.5 ppm)	Chronic 7 days - 12 months 6 - 26 hrs/day	Mouse	Decreased resistance to K. pneumoniae infection, decreased lung clearance rate; both significant after at least 3 months exposure	[48]
1.9 mg/m^3 (1 ppm)	Acute 1 hour	Rabbit	Reversible structural changes of structural proteins (lung collagen & elastin)	[35]
3 - 3.8 mg/m^3 (1.6 - 2 ppm)	Acute 30 inhalations	Man	Significant increase in air passage resistance at 23%	[17]
3.76 mg/m^3 (2 ppm)	Chronic Life-long 24 hrs/day	Rat	Loss of cilia, 30% enlargement of cells in bronchial epithelium Interpretation: early stages of emphysema	[40, 42]
4.7 mg/m^3 (2.5 ppm)	Chronic 3 - 5 yrs 8 hrs/day	Man	Emphysema and chronic bronchitis No diagnostic criteria	[14]

(Table concluded on following page)

TABLE 11. (concluded)

NO_2 concentration	Exposure length, mode	Species	Effect	Source
4.7 mg/m^3 (2.5 ppm)	Acute 6 hrs	Mouse	Increased resistsnce to subsequent NO_2 stress. Histological interpretation: inflammatory reaction of lung tissue	[33a]
7.5 mg/m^3 (4 ppm)	Acute 15 minutes	Man Man	Significant decrease in arterial partial O_2 pressure at 8.3%. Completely reversible	[17]
9.4 mg/m^3 (5 ppm)	Chronic 2 months 24 hrs/day	Squirrel monkey	Decreased resistance to bacterial and viral infection	[49]
9.4 mg/m^3 (5 ppm)	Acute 4 hours	Guinea pig	Reversible rise in respiration frequency of 20%, with simultaneous decrease in breath volume	[9]

resistance to infection caused by NO_2 [Ehrlich and Henry, 48; Henry et al., 49]. We can, therefore, regard the present epidemiological data on long-term effects of low NO_2 concentrations on pulmonary functions and diseases of the air passages as relevant.

Experimental results on the impact of exposure cycles are contradictory. Long-term exposures of mice to relatively high NO_2 concentrations of approximately 76 mg/m^3 [Ross and Henschler, 30] showed that the extent of the effects (pathologic reaction of lung tissue, including benign adenomas) increased with the length of exposure-free intervals, i.e., that dosage (c × t) and damage to the lung are negatively correlated. In contrast, chronic exposure experiments, also on mice, to concentrations of approximately 0.94 mg/m^3 (0.5 ppm) showed that chronic-continuous exposure (24 hrs/day) had a greater effect on resistance to infection, lung clearance rate [Ehrlich and Henry, 48], and on the histopathological condition of bronchial epithelium [Blair et al., 39] than did a chronic-intermittent (6 and 18 hrs/day) exposure, i.e., that dosage correlates positively with damage. Wands [53] arrives at the same conclusion on the basis of a literature survey. Since the last-listed studies, however, approach actual immission conditions, it will behoove us to apply particularly stringent limits to the parameter for long-term exposures (MIK_D value).

In regard to the nuisance-value aspect, we can confine ourselves to the odor nuisance, since irritation of the mucosa in the upper air passage and other subjective symptoms show no clear-cut relation to concentration [Henschler et al., 22]; habituation plays a large role in these respects. The parameter for short-term exposure should, therefore, lie below the threshold for odor perception (MIK_K value). Brief transgressions beyond the MIK_K value can be regarded as insignificant when breathing impairment and/or odor nuisance can definitely not occur.

The requisite demands are met by the following limiting values for NO_2:

MIK_D (24 h): 0,1 mg/m^3 (0,05 ppm)
MIK_K (30 min): 0,2 mg/m^3 (0,1 ppm)

A brief (maximally, 90 seconds) period of exceeding the MIK_K value up to 1 mg/m^3 (0.53 ppm) seems medically-biologically insignificant, since according to present findings [v. Nieding et al., 16], even sensitive people definitely do not suffer any increased air passage resistance at such concentrations.

If we assume the ratio in immission concentrations of $NO : NO_2 = 5 : 1$ (which, in spite of diurnal variations, is realistic), we obtain the following limiting values for NO:

MIK_D (24 g): 0,5 mg/m^3 (0,4 ppm)
MIK_K (30 min): 1,0 mg/m^3 (0,8 ppm)

A brief (maximally, 90 seconds) period of exceeding the MIK_K value up to 5 mg/m^3 (4.1 ppm) seems medically and biologically insignificant. The parameters listed will positively not lead to a significant increase in the biological MeHb base level.

6.3. Lead Compounds

6.3.1. Introductory remarks

The symptoms of lead poisoning were described as early as Hippocrates [Aub et al., 1]. In the 18th century — at the latest — typical signs of poisoning were associated with lead absorption.

Lead enters the body either through the digestive tract or the lungs, and passes into the blood circulatory system. Cutaneous lead absorption was possible in past decades due to the use of lead-containing salves, but no longer plays a role. It can occur today by means of contact with organic lead compounds, but needs to be considered only in exceptional special work situations.

The addition of lead to internal combustion engine fuels leads to lead emission, which enters man primarily through inhalation. In judging the significance of leaded fuels for human health, we must also consider lead intake from other sources as far as large elements of the population are concerned; lead exposure due to specific work situations or accidents is not within our scope.

In order to discuss the contribution of lead from sources in "normal" life to lead metabolism, we first offer a survey of the lead content of air and foods; then we shall discuss the essential physiological processes and problems of pulmonary and visceral lead absorption, distribution, and elimination. Further sections will deal with the symptoms of lead poisoning as observed in occupational medicine and in accidents of the population at large. In the last section, we shall treat data offering a basis for the range of biological stress in the normal population. This will be followed by evaluations of the dangers to public health due to lead absorption, and the basis for a parameter for atmospheric lead content.

6.3.2. Lead concentrations in the human environment

6.3.2.1. Lead content of the air

Chemical compounds of atmospheric lead

Combustion in the automobile engine converts the lead hydrocarbons added to fuel into lead oxide. Since ethylene dibromide and ethylene dichloride are also added to fuel, lead is also converted to lead halides. Sulfur compounds present in lead as natural impurities (maximum, approximately 0.01 - 0.1 weight %) yield sulfites, which give rise to lead sulfates [Brunner, 10]. The inorganic compounds, however, are not only emitted as such, but are also converted to more or less stable complex compounds. In addition, air contains uncombusted tetraethyl and tetramethyl lead expelled in the exhaust. The lead derived from the burning of coal is bonded to silicates.

Lead concentrations in the air

Data on atmospheric lead content nearly always refer to inorganic lead which is present in particle form. Due to their high volatility, organic lead compounds are not captured by the sampling filters. To judge from the reports of Lutmer et al. [60], the ratio of organic to inorganic lead is approximately 1 : 30. In spite of its greater toxicity, therefore, organic lead is supposedly insignificant. Measurements of Laveskog [51] in a main street of Stockholm show the ratio of alkylic to particulate lead as 1 : 10. At least in auto repair shops, however, organic lead compounds can be significant: Preis (quoted in Högger [36]) found in 8 repair shops an average of 14 μg Pb/m^3 as dust, and an additional 15 μg Pb/m^3 as tetraethyl lead vapor.

There are numerous measurements of particulate lean concentrations in the open atmosphere. They have, however, the disadvantage of having been taken under very different and hardly comparable conditions. For a medical assessment of lead stress, the measurements should permit the most precise conclusions possible concerning the amounts of lead actually inhaled in given work or living situations. Data on diurnal and annual averages, not measured immediately at the edge of the road, are, therefore, most suitable for that purpose. But the examination of many varied values will at least lead to a survey of lead emission, even if the differences in methods and local conditions will not permit us to generalize from any one single result.

Atmospheric lead concentrations were summarized by Lahmann and Möller [50]. Others are:

Colucci, Begemann and Kumler [14] measured annual averages at 12 sites in Detroit, New York, and Los Angeles, mostly at a distance of a few meters from traffic. Their values ranged from 1.2 - 11.3 μg/m^3; most of them fell between 4 and 7 μg/m^3; daytime concentrations were approximately 40% higher than nocturnal, higher in fall and winter than in spring and summer, and higher near freeways than in city streets. Ludwig et al. [59] obtained considerably lower annual averages from an analysis of a total of 20 test sites in 3 cities: Cincinnati — 1 - 2 μg/m^3, Philadelphia — 1 - 3 μg/m^3, Los Angeles — 2-3 g/m^3. Lahmann and Möeller [50] in 1966/67 obtained data from 3 meters above a heavily travelled street in Berlin; the annual average was 3.8 μg/m^3. In 1970, Jutzi [39] measured the lead content at 7 test sites in Zurich, and obtained an average of 3.8 μg/m^3 — which was 40% higher than the value of 2.7 μg/m^3 from the same test sites in 1963. This, however, pertains to measurements at certain hours of the day; the relevant daily averages might well be considerably lower.

It can be assumed, as a starting point, that the urban lead content remote from traffic lies between 0.1 and 1.0 μg/m^3 of air. The relationship of lead content to traffic density, distance from the roadway, and climatic conditions was investigated by several authors. Some examples follow below:

Figure 1 shows lead concentration at the edge of the roadway and at a distance of 10 meters during the course of the day, plotted against traffic density.

Figure 2 shows the drop in lead content with increased distance from the roadway, and for varying traffic density.

Figure 3 shows the annual variation in atmospheric lead content. It has been described several times (e.g., Chow and Earl [12]; Colucci et al. [14]; Jost [38]) and is attributed to climatic changes. Results may, therefore, show geographic variation as well.

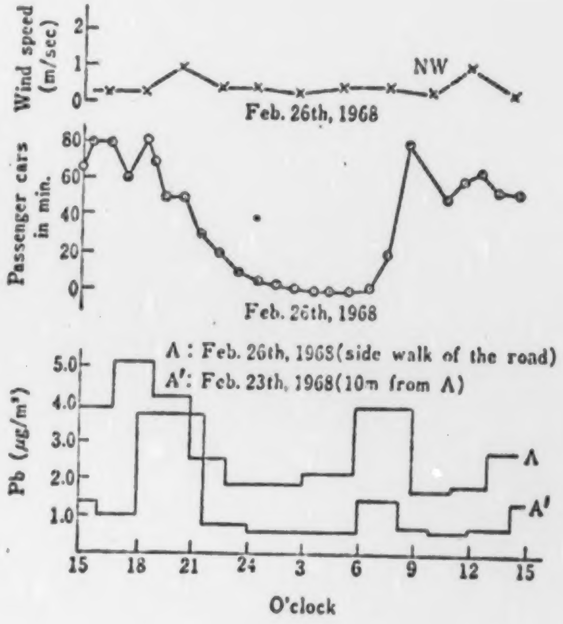


Figure 1. (from Kobayashi et al. [48])

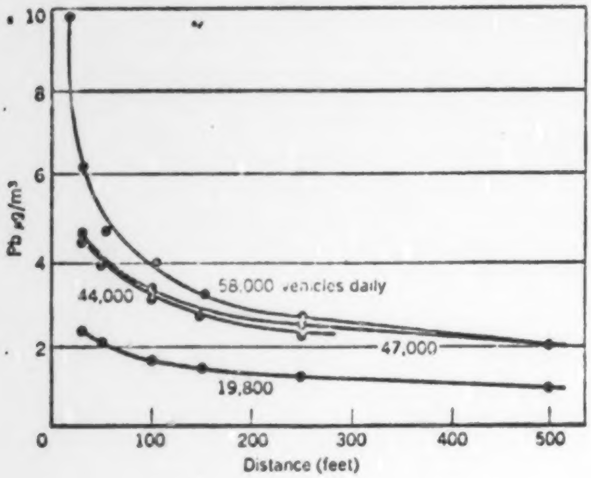


Figure 2. (from Daines et al. [16])

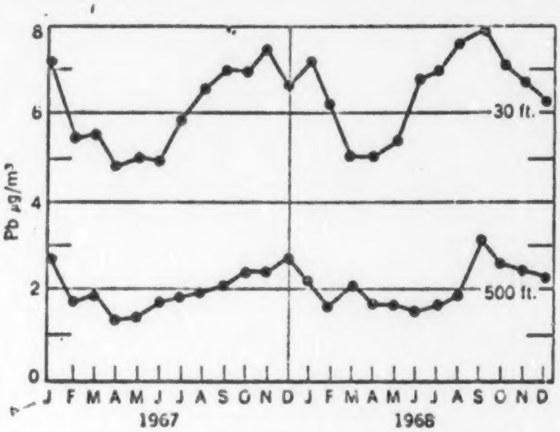


Figure 3. (from Daines et al. [16])

In several regions above the Pacific Ocean, Chow et al. [13] measured lead concentrations of 0.0003 to 0.0015 µg/m3.

Size of lead particles in the atmosphere

The size of particles collected depends among other factors on their source; larger particles settle out rather quickly, while those < 5 µm are called aerosols, and are transported by air currents. According to Hirschler and Gilbert (30), in typical city traffic, one half to two thirds of the particles emitted and collected at the exhaust are < 5 µm. In individual cases, size depends largely on the age of the engine and the nature of the traffic. In city traffic, only half of the lead burned at any given moment is given off into the atmosphere; with greater speeds or acceleration, a part of the retained lead breaks free and is expelled in large particles.

Habibi [25] and TerHaar et al. [87] have reported further investigations on expulsion and size of lead and other particles in exhaust gases under various conditions. We need not discuss them here in detail, since measurements at the exhaust are less relevant for assessment of health impact.

Robinson and Ludwig [74], collecting dust samples in several American cities, found that almost all lead particles were < 1 μm (aerodynamic diameter); 75% of the sample had a diameter of < 0.5 μm. The Swiss Tetraethyl Lead Commission [6] came to the conclusion that the greater portion of the expelled lead particles measured less than 0.125 μm in diameter. Lee et al. [53] found that 95% of particulate lead had an aerodynamic diameter of less than 0.5 μm. According to Hasegawa et al. (quoted in Horiuchi [33]), 99% of the inorganic lead compounds in exhaust gases are smaller than 2 μm. In contrast to these findings, Daines et al. [16] list higher particle sizes: 65% < 2 μm, 85% < 4 μm. On the basis of their electron-micrographs, Lawther et al. [52] recently emphasized that the irregular shape of the particles preclude clear-cut conclusions as to their aerodynamic diameter.

Sources of atmospheric lead

Other sources besides exhaust gases contribute to lead in the atmosphere: the lead industry, as well as combustion of coal and fuel oil. Industrial facilities certainly will have local significance, but are comparatively rare; they cannot be held responsible for atmospheric lead beyond a certain range. Coal and fuel oil also contain lead; but their contribution to lead emission in the U.S.A. during 1968, according to McMullen et al. (quoted in Engel et al. [19]), amounted to only 0.5 and 0.01%. Even if these values should be too low, it is the automobile exhaust gases which represent by far the most significant source of lead emission.

Since lead arsenates are no longer used as sprays in tobacco cultivation, the lead content of tobacco smoke has dropped significantly [Weber, 92]. According to Weber, the lead content in the smoke from one cigarette is below 0.1 μg.

6.3.2.2. Lead content of soils, water, plants, and foods

Mathess [63] has compiled a literature survey of lead measurements for minerals, soils, and ground water. According to this, soils average from 10 - 40 mg/kg total value, but may exceed 100 mg/kg. The soluble components are much lower. Extremely high values are encountered in soils having minerals containing lead ore as substrate. Near an ore vein in the Sauerland, the lead content of soils was 15,000 mg/kg. According to Kempf [46], the lead content of groundwater in granite ranges with lead deposits — e.g., in the Harz, the Sauerland, and the Eiffel regions — ranges from 0.1 - 0.5 mg/l, while groundwater ordinarily contains 0.001 - 0.060 mg/l and sea water — 0.0008 - 0.008 mg/l.

Apart from these figures, which are independent of human activity, the heavy metal may also leach from lead-containing pipes into the water, and there accumulate to above 1 mg/l.

In past times, the use of lead arsenate as agricultural spray could also raise the lead content of soils.

Next to roads with heavy traffic, the lead in exhaust gases may distinctly raise the lead concentration in soils. Hellenz (quoted in Mathess [63]) analyzed soils beside the Giessen/Frankfurt a.M. freeway near the Butzbach exit. He found, however, that concentration dropped rapidly with increased distance from the roadway. The following values were obtained in air-dried soils:

Distance from roadway, m	Lead extracted with HCl, mg/kg
0 (planted parkway)	147
0 (planted parkway, depth of 20-40 cm)	25
0 (edge of roadway)	130
20	26
50	23
100	19

Next to old or especially heavily travelled roads, the lead content of soils may be considerably higher. Values obtained by Singer and Hanson (in Mathess [63]) average 245 mg/kg, ranging from 128 - 700 mg/kg. Similar values were measured by Chow [11] next to U. S. Highway 1. The lead content of dry grass in a strip 15 meters wide next to the roadway ranged from 40 - 60 mg/kg.

As the above values show, lead settling out from exhaust gases enters the soil very slowly. Obviously, the easily soluble lead halides combine with the SO_4^{--} and CO_3^{--} ions in the soil to form compounds with low solubility, i.e., fairly immobile compounds. This may be the reason that up to now no noticeable accumulations of lead were found in root vegetables grown next to streets and roads. Under laboratory conditions, a limited lead intake from high-lead soils was reported in roots (Zuber et al., in Högger [36]). The authors state that under conditions in the field, the lead content of soils would be too low to result in significant absorption by the roots.

In contrast, the increase in the above-ground portions of plants due to lead dust from exhaust is very evident. It has been researched by Leh [54], Page et al. [69], Bovay [8], and Keller [45, 46], who tested its relationship to distance from the roadway. These extensive analyses cannot be discussed here in detail. Some tables and figures are given below.

TABLE 1. LEAD CONTENT OF POTATOES VS. DISTANCE OF PLANT LOCATION
(in ppm dry weight) (from Leh [54])

Distance	Leaves		Tubers (peeled)	Peels (washed)
	Unwashed	Washed		
5 m	42 - 65	38 - 42	1,4 - 1,8	2,7 - 4,6
10 m	32 - 43	35 - 41	2,0 - 2,6	2,1 - 2,8
50 m	19 - 38	15 - 36	1,5 - 2,6	2,2 - 4,6
100 m	9 - 30	8 - 27	1,1 - 5,4	0,9 - 4,1

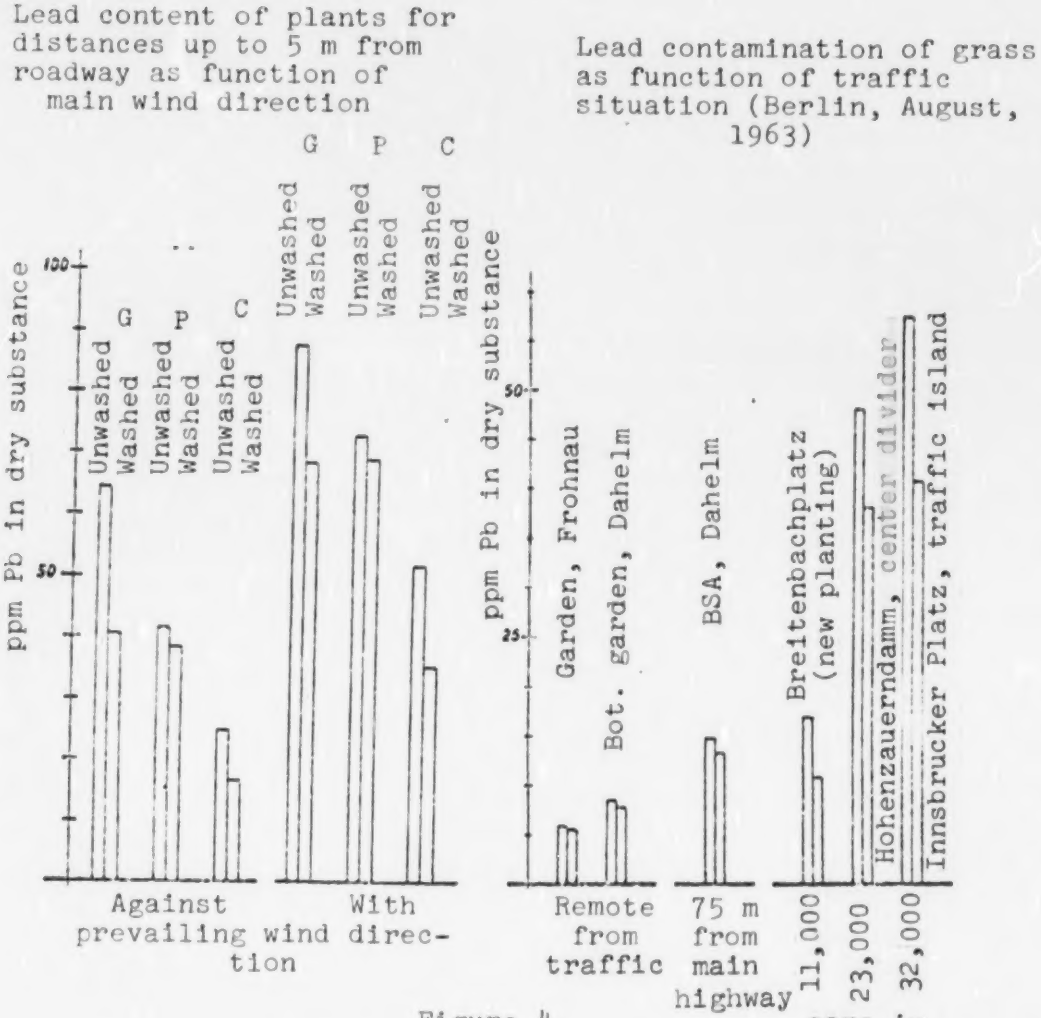


Figure 4.

G — grass, P — potato plant; C — carrot leaves

Plants or plant portions with a tomentose surface or comparatively high surface-weight ratios are especially contaminated, e.g., grass, beet leaves, lettuce or spinach. Grains, on the other hand, are well protected by their awns. Closed-type cabbage varieties and fruits absorb little lead. At sites remote from traffic, grass has a lead content of up to 10 mg/kg dry weight; adjacent to the roadway, it can contain as much as 100 mg/kg lead [Bovay, 8].

Ter Haar [86] analyzed 10 field-grown fruit varieties, planted next to a roadway or in greenhouses with lead-containing air. In 8 varieties, he found no rise in lead content of edible plant portions; the non-edible portions, however, registered 2 - 3 times the concentration of control plants grown in greenhouses with filtered air.

A part of the lead deposited on plants can be washed off; but this component is highly variable due to several factors, such as surface condition, exposure time, etc.

Independent of traffic, plants near industries using lead can show very high concentrations because of the lead dust which settles on them; locally, this may be much more significant than the lead from exhaust gases.

(The quantities absorbed daily from food and drink are discussed later in the section "Absorption through the gastrointestinal tract.)

6.3.3. Physiological processes of lead absorption by the body

6.3.3.1. Absorption through the lungs

Inorganic lead compounds are inhaled as solid particles. We shall begin by tracing the path of an inhaled particle:

Either it leaves the body again at once during exhalation, or it settles on the wall of the air passage. This is called deposition. The portion of the air passage in which it is deposited decides the further fate of the deposited particle. Those landing in the nose, pharynx, trachea, or bronchi are usually carried — within hours — back upwards by the cilia which cover these portions and reach the esophagus. If they are easily soluble, they may be absorbed in the upper respiratory tract. Material deposited deeply in the lung (bronchioli terminales, alveoli), i.e., *in portions* without ciliated epithelium, may remain there for months if it is not dissolved. Macrophages (phagocytes) or Brownian movement may eventually transport it from the alveoli back onto the ciliated epithelium, from where it is eliminated to the esophagus via the bronchi. If this bronchial elimination does not occur, the material is absorbed into the interior of the body proper. Depending on its solubility, it can pass more or less rapidly into body fluids (lymph or blood) or be deposited as particles in the interstitial lung tissue. From there, absorption may occur, or it can be transported to the lymph nodes; finally, it reaches the blood stream and, hence, other organs.

Deposition of lead dust in the lungs

Particle size considerably influences the quantity and location of dust absorption; it is also affected by the depth and frequency of respiration. The numerous unsolved problems pertaining to this issue cannot be discussed in detail here. Figures 5 and 6 (from Walkenhorst [91], and the Task Group of Lung Dynamics [17]) clearly show that it is far from easy to calculate the amount deposited from inhaled dust, which usually has a broad range of particle sizes; it must more or less be estimated. The conditions for particles below 1 μm, which constitute probably by far the largest portion of air-borne lead pollution, are particularly unclear.

Various authors performed inhalation experiments and report that 25 - 60 weight % of the deposits from lead dust below 1 μm is given off to the tissues (Table 2).

Lead absorption in the lungs

What happens to dust deposited after inhalation depends mostly on its solubility in the respiratory passages. There are no experiments dealing with the solubility of various lead compounds in the fluid film lining the respiratory passages. It varies greatly

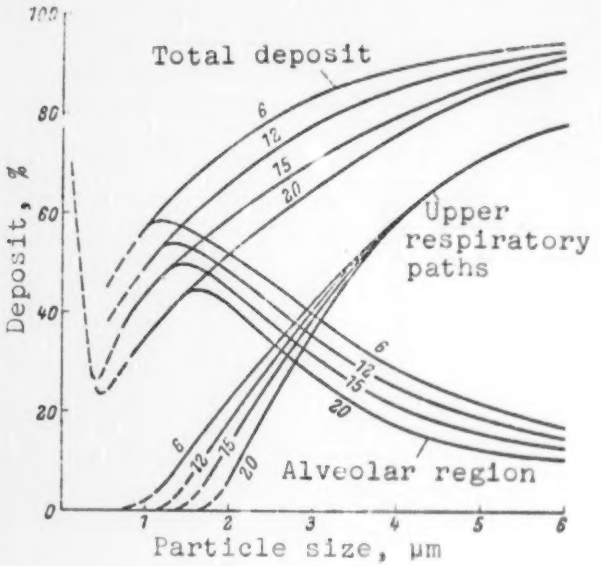


Figure 5. Proposed curves (using experimental and theoretical data) for total deposition, deposition in the upper respiratory tract, and in the alveolar region vs. respiratory frequency. The numbers on the curves indicate the frequency of respiration (from Walkenhorst [91])

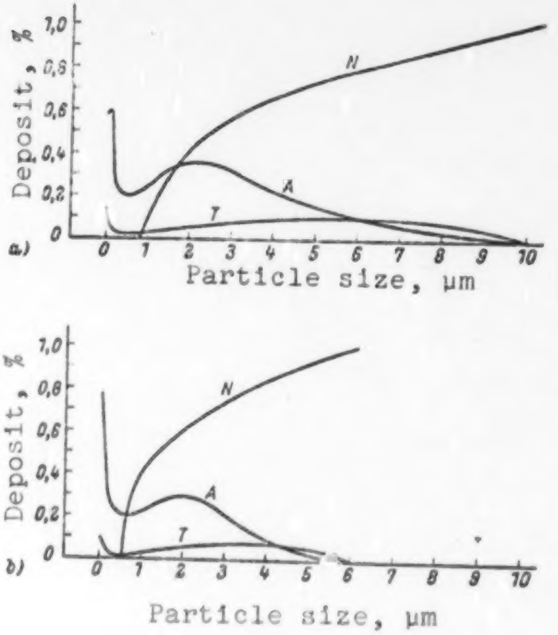


Figure 6. Results of the American Task Group [17]. Respiration frequency 15/min. a) volume 750 mg (11.2 l/min); b) volume 2150 ml (32.3 l/min):

A — alveolar region; N — nasopharyngeal region; T — tracheal-bronchial region (from Walkenhorst [91])

in water, and can increase or decrease in several physiological fluids (cf. section "Daily lead absorption from food and drink"). Lead oxide, for instance, is 70 times more soluble in serum than in water (Pleissner, quoted in Aub et al. [1]).

Obviously, in the respiratory passages, the solubility and intake into the blood of lead and its compounds is far greater than its low solubility in water would suggest. Even Minot (in Aub et al. [1]) proves by experiments on cats that "insoluble" compounds are easily absorbed in the lungs. Blumgard (in Aub et al. [1]) showed on dogs that lead carbonate, fairly insoluble in water, can be absorbed even from the pharynx after an extended period of time.

TABLE 2. DEPOSITS OF LEAD DUST IN THE RESPIRATORY PASSAGES

Particle size in µm	Deposit in % of amount inhaled	Author
0.05	35	Kehoe [42]
0.75	54	Kehoe [42]
0.9 - 1.2	43 - 53	Kehoe [42]
0.125	ca. 60	Swiss Commission on Leaded Fuels [6]
No data	39 - 47	Mehany [65]
Average 0.23	27	Hursh and Mercer [34]
0.02	62	Hursh and Mercer [34]
0.05 - 0.5	34 and 60	Booker et al. [7]
Vapor	99	Booker et al. [7]
1	63	Nozaki [68]
0.05	42	Nozaki [68]

Kehoe [42] emphasized the complete and rapid absorption of lead sesqui-oxide in his experiments when the particles were < 1 µm. From lead acetate inhalation experiments by two subjects (Horiuchi et al. [31]), it could be calculated that approximately 80% of the amount deposited in the respiratory passages was absorbed. Booker et al. [7] tested the inhalation of radioactive lead aerosols with a particle size from 0.05 - 0.5 µm; in man, approximately half the amount deposited was absorbed. Hursch and Mercer [34] list the half-life as 6 1/2 hours. Using rats and domestic animals, Sattler [75] determined the halflife of inhaled lead particles to be only 30 - 33 minutes. Pott and Brockhaus [70] found that after intratracheal injection of lead bromide and lead oxide, just as much lead found its way into the bones as after intravenous injection.

The experiments of Smith et al. [83] point out that lead from automobile exhaust gas significantly raises the lead deposits in the body, i.e., that a significant percentage is deposited in the lungs and there absorbed. In guinea pigs and rats, the authors noticed a considerable increase of lead in the bones after 4-year inhalation of air (in Detroit) containing an average lead content of 2.5 μg/m^3; in rats, the average value was 64%, in guinea pigs — 31%. Tests on mice by Luther et al. [60] showed the same tendency for 2.6 μg lead/m^3; due to the relatively short testing period (15 months), the differences were not statistically significant.

The above experiments indicate clearly that the surface of the respiratory passages offers very good possibilities for the solution of even nearly water-insoluble lead compounds. This may be due to the chemical composition of the fluid film moistening the respiratory passages; the very large total area of the alveoli (35 - 75 square meters) [Schmidt, 78] in close contact with the circulation also offers very good possibilities for transfer and exchange.

The rate at which lead compounds inhaled with aerosols dissolve in the lungs is, at present, still quite uncertain. Preis (in Högger [36]) finds that lead from street dust dissolves only with great difficulty, which may be due to its being mixed with oil particles. But street dust must not be equated with fine dust of < 5 μm; besides, oil particles also are easily absorbed by the lungs [Schlipköter et al, 82]. In view of all the results given above, it can be assumed that absorption of lead inhaled in urban areas occurs within a few days. In this assumption, only a small role is played by the slow bronchial lung clearance of particles deposited in the terminal respiratory passages.

Haley's [27] assertion that lead particles from automobile exhaust gas emissions are, for practical purposes, insoluble and are bronchially eliminated after deposition, finds no support. He lists no experiments refuting the opposite evidence from many sources. Dabelstein [15] also recently asserted — citing no references — it had been recently shown that lead particles are not (as was assumed earlier) absorbed in the lungs, but are instead removed from the lungs by the sputum.

Estimating the amount of lead absorbed by the lungs after inhalation of automobile exhaust gas emissions containing lead

A summary of the above data, experiments and theoretical considerations reveals that insufficient information is available on many details concerning the constitution of lead dust, as well as the deposition, elimination and absorption of lead in the lungs. We can, therefore, not offer any scientifically exact calculations for the separate stages, but must be content with a preliminary estimate of the various factors on the basis of present-day knowledge.

1. Atmospheric lead content: we assume a daily average of 1 µg lead/m^3 air. Absorption values for other concentrations at various sites can be easily calculated on that basis.

2. Particle size: since for by far the largest part of the day dust is not inhaled immediately at the roadside, we can assume that all particles are < 1 µm, and that most of them are < 0.5 µm.

3. Deposition: the deposition of these small particles occurs nearly entirely in the terminal air passages. Graphic representation shows a minimum at approximately 0.5 µm, and rises steeply with decreasing particle size (cf.,Figure 4 and 5). Based on these data and experimental results, we estimate that 40% of the inhaled amount is deposited.

4. Respiratory volume: we assume a volume of 15 m^3/day.

5. Respiratory frequency, depth of respiration: variations in these functions, especially during physical labor, certainly affect the deposition of aerosols; but their effect is hard to estimate. The lower

deposition rate for higher breath/minute volumes might be due to increased ventilation.

6. Solubility of lead particles: it might be somewhat lower than that of the compounds absorbed into the blood within hours during the inhalation tests. We assume that within a few days,small lead particles are completely dissolved in the alveolar milieu.

7. Bronchial elimination: bronchial lung clearance has scarcely any significance, since only particles < 1 μm are deposited in the terminal air passages, and are dissolved within a few days. We estimate it to be approximately 10%, with a maximum of 20%.

8. Lead dust storage in the lung: does not take place due to a high solubility under physiological conditions.

9. Lead absorption: the estimated values indicate at least 80% absorption of the deposited lead dust.

Totals

Atmospheric lead content	1	μg/m^3
Breath volume	15	m^3/day
Inhaled lead quantity	15	μg/day
Lung lead content with 40% deposition	6	μg/day
Amount of lead re-absorbed with 80% absorption	4.8	μg/day
Amount re-absorbed via viscera for 10% absorption after bronchial elimination of 1.2 μg Pb/day	0.12	μg/day

Given the above conditions and a site with an atmospheric lead content of 1 μg/m^3, an average of approximately 5 μg lead is absorbed daily through the lungs.

6.3.2. Lead absorption through the gastrointestinal tract. Daily additional lead from food and drink

Several authors have measured the lead content of foods. Taking the consumer's diet choices into consideration, the average daily amounts from food and drink were calculated. Kehoe [40] assumes the oral intake for the North American to be 300 μg (120 - 350 μg); Horiuchi [32, 33] — 250 μg (230 - 320 μg) for the Japanese; Lehnert et al. [56] — 518 μg for the Germans. Leh [54], however, states an oral intake of 1500 μg (1200 - 2200 μg) daily on the basis of his analysis, i.e., a value much higher than any of the others. On the same basis, Kloke et al. [47] give the same results.

Lead intake can vary with lead content and quantity of food consumed.

Enteral lead absorption

According to Kehoe [22], only about 5 - 10% of the lead intake from food and drink reach the blood. Horiuchi [33] gives the same values for tests run in Japan. Hursh and Suomela [35] measured enteral absorption of radioactive lead on three subjects; they obtained values of 1.3, 8.1, and 16%. Imamura [37] reports the relatively high value of 30%; however, he used lead acetate, which is very soluble in an alkaline medium.

(Since the absorption rate is based on the difference between lead intake from food and lead elimination through the feces, it disregards the component which is absorbed initially, only to be eventually returned to the entera via the bile.)

Pott and Brockhaus [70] administered lead bromide and Pb oxide orally to rats; they found that the lead content of bones subsequently was between 2.0 - 6.8% of that obtained by comparable intravenous injections. Sattler [75] also obtained enteral absorption values of 6% in animal experiments.

Absorption rates from 5 - 10% are clearly "normal"; rat experiments by Milev et al. [66], however, showed that they can be increased 7 times by changes in the protein content of the diet. A 3-day low-calorie diet also resulted in a 7-times higher absorption than that of the controls. Kostial et al. [49], using rats a few days old, found increased absorption levels from the entera of 55%.

The much lower absorption from the entera compared with that from the lungs is probably due to the fact that the solubility of many lead compounds drops sharply in an alkaline medium (Table 3).

A diet low in calcium raises lead absorption (Sick and Goyer; Lederer and Hernberg).

A diet rich in calcium and phosphorus lowers the absorption rate.

TABLE 3. SOLUBILITY OF SOME LEAD COMPOUNDS FOR ARTIFICIAL GASTROINTESTINAL FLUIDS

(from Horiuchi [33])

Lead cmpounds	Solubility (%)		
	Waters	Gastric juice*	Intestinal juice**
1) Lead sulfide	1.6	10.0	0.7
2) Lead sulfate	13.6	64.3	1.0
3) lead monoxide	0.5	90.7	0.5
4) Lead chloride	97.4	98.4	0.6
5) Basic lead carbonate	0.8	96.1	3.1
6) Lead acetate	99.0	99.6	17.4
7) Lead stearate	0.4	37.8	3.9

Note: *Mix conc. HCl (0.4 ml) and saccharated pepsin (0.25 g), make to 100 ml with destilled water. pH:1.47.
**Take $NaHCO_3$ (1.5 g) and pancreatin (0.28 g), add dest. water to make 100 ml. pH : 8.30.
ᵴpH of water is 4.89.

According to this, the absorption rate in the entera depends largely on the pH value in the duodenum.

Estimates of the quantity of lead absorbed daily in the entera

In estimating the quantity of lead absorbed from the diet per day, we base our calculations on the value of Kehoe's (300 µg), which is most frequently used in the secondary literature.

If we assume that 10% of the amount offered by the daily diet is absorbed, we arrive at a daily intake of 30 µg Pb/day from food.

6.3.3. Distribution of lead in the body

After intake in the blood, lead is bound primarily to the hemoglobin in red blood cells [Barltrop and Smith, 2], is mainly stored in the liver and kidneys and, after a period of hours or days, is excreted from those organs; or it can be transported to the bones and deposited there for a long-term period. It is bone tissue which is the primary deposition site for lead; in the course of the slow but constant bone metabolism, some may be dissolved out again, but a larger amount is constantly re-deposited. In the course of a lifetime, therefore, lead content of skeletal tissue constantly rises by virtue of contributions from the daily diet alone. Schroeder and Tipton [79] determined the lead content of 150 North American accident victims. In 80%, it lay between 50 and 200 mg; 91% of the total was deposited in the skeleton. Lead deposits rose up to an age of 60 - 70. Barry and Mossman [3] also found that total lead in the body rose with age; in men between 60 - 70 (assuming a body weight of 70 kg), it amounted to 263 mg; in women of the same age range — 152 mg; approximately 95% was contained in the bone tissue. In metabolic studies on 5 subjects, Thompson [89] found that between 12 - 28 days, with an average intake of 274 µg Pb from the diet, 10 µg/day were not excreted in feces or urine. Using those values, approximately 180 mg lead is stored in the body during a 50-year period — a quantity which corresponds well to results from tissue analysis.

Lead accumulation in bone tissue of that order is probably not accompanied by an equal rise in blood concentrations A 10 - 40 µg/100 ml level is a "normal" blood lead level; but this figure does not reveal the amounts deposited. Based on his many-sided investigations, Kehoe states that even an urban dweller, who absorbs 20 µg Pb daily from the lungs, maintains this balance; increased lead intake is supposedly balanced by increased lead excretion; depending on the individual, a balance between intake and excretion is maintained between 15 - 40 µg/100 ml. Kehoe [40] also assumes that under these "normal" conditions, the body builds up a deposit of 100 - 400 mg of lead.

6.3.4. Lead excretion

Lead is excreted via the feces, urine, and perspiration. The feces contain by far the largest quantity; only a small part of this, however, has been metabolized — most of the lead intake passes through the gastrointestinal tract without having been absorbed. Possibly, the quantity of lead passing into the intestines via the blood and bile is equal to that excreted by the kidneys. Sweat glands, too, play a part in lead excretion.

6.3.5. Pathological effects of lead

6.3.5.1. Clinical symptoms of lead poisoning

Acute lead poisoning ending in death rarely occurs today.

Symptoms of chronic lead poisoning as it occurs in workers in the lead industry mostly have a gradual onset [Buckup, 85; Moeschlin, 67]: overall gastrointestinal tract instability, loss of appetite, stomach pains, constipation, fatigue, general weakness, dizziness, headaches — especially in the forehead and temple region; in later stages, there are colic-like intestinal pain (lead-colic), ash-gray, sub-icteric facial paleness ("leaden color"), rarely also a blackish-blue line at the gumline ("lead edge"). Finally, paralysis of the peripheral motor nerves can occur, mostly in the area of the Nervus radialis ("droop hand"); inflammation of the stomach lining, spastic contractions of the arterioles, with a slight rise in blood pressure, possibly kidney damage. In children, particularly, brain impairment ("lead encephalitis") with loss of consciousness, convulsions and coma can be observed. It is still uncertain whether lead can also cause arteriosclerosis. Studies reporting a rise in the rate of miscarriages, premature or still births seem convincing (Menyasz et al. [64]).

6.3.5.2. Lead-induced biochemical changes

The toxic effects are probably due to bonding to cellular enzymes by means of a heavy-metal-ion exchange, or bonding to the sulfhydril (HS) groups of the enzymes (Buckup [85]).

Most of the work concerning lead effects has emphasized the porphyrin metabolism and hemosynthesis. Figure 7 shows at which points of the cycle enzymatic blockage due to lead occurs.

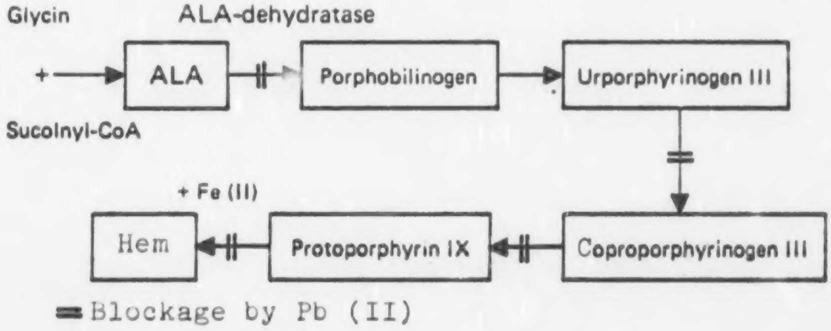


Figure 7. Enzyme blockage by PB (II) in hemoglobin synthesis (from Lehnert et al. [ ]*)

*Translator's note: Reference number inadvertently omitted in original foreign text

The consequence is a loss of activity of delta-amino-levulinic acid dehydratase (ALA-D) in blood (a symptom specific for lead!), and a rise in excretion of delta-amino-levulinic acid and coproporphyrin in the urine. According to Hernberg and Nikkanen

[29], ALA-D is especially sensitive to lead stress. Haas et al. [23] found that ALA excretion in the urine, as well as ALA concentrations in the blood, correlated equally well with the Pb blood level when this exceeded certain norms.

Anemia is a significant consequence of an impaired hemosynthesis. A typical symptom is a rise in basophile dotted erythrocytes ("stippling cells").

DeBruin [9] reports a number of further biochemical effects of lead.

In lead poisoning, the lead level in the blood rises (mostly to above 70 - 80 µg/100 ml blood). A raised blood lead level per se, however, even of 100 µg%, is not necessarily associated with toxic symptoms. The same holds true for lead in the urine: it, too, merely indicates the extent of lead metabolism. Observations on workers in the lead industry indicate that a rapid rise in blood and urine concentrations (as for instance during the first few weeks of exposure) is more prone to elicit toxic symptoms than a gradual increase. Blood levels of below 70 µg/100 ml, therefore, do not necessarily preclude lead poisoning. Obviously, the body can adapt itself to a gradual rise in lead levels [Lehnert et al., 57]. Most writers regard the lead stored in bone tissue as tertiary lead phosphate as inactive, but as "available" at all times [Buckup, 85], either through fever and by calcium deficiency [Moeschlin, 67]; even years after illness due to lead poisoning it can lead to a rise in lead excretion [Prerovska and Teisinger, 71] and to a relapse [Fuchs, 21]. The significance of this important process precisely for the "normally" stressed individual, however, is as yet unknown.

A number of the effects of lead, based on various observations, has been discussed, without any definite conclusions as to their significance in man. Among these are the cytotoxic effects of lead in cell cultures [Beck, 5], which could impair lung clearance rates for other dusts; damage to leucocytes [Sawinski et al., 76], as well as teratogenic [Ferm and Ferm, 20] and mutagenic [Schwanitz et al., 81] effects. In this connection, we also need to mention possible lowering of resistance against infection [Hemphill et al, 28].

6.3.6. Limits of biological stress due to lead

6.3.6.1. Biological criteria for the biological stress limit

For the general population, the limits of tolerable lead intake are to be set at a dosage which, after decades of exposure, does not cause any noticeable damage even in vulnerable individuals. At the present time, the most sensitive indicators for suspecting lead damage are: a rise in excretion of ALA and coproporphyrin in the urine, a drop of ALA-dehydratase activity in the blood, and a rise in blood lead level. It is also important to determine whether the amount of lead deposited in the body is increasing under the existing or potential lead stress.

6.3.6.2. Determination of tolerance limits for daily lead intake on the basis of public health or experimental investigations

Kehoe [42] administered various dosages of lead (3000, 2000, 1000, and 300 μg/day) to four subjects, in addition to that of the daily food intake, and measured blood levels and excretion. After 4 months, the daily lead intake of 3.27 mg (0.27 mg of it in the normal diet) resulted in a 80 μg/l of lead excreted in the urine, a blood level of 50 μg/100 ml, and to a lead deposition of 55 mg. Kehoe estimates that the "danger point", i.e., a blood level of 80 μg/100 ml, would have been reached after 4 further months of this experiment. On the basis of a two-year experiment with 2.35 μg/day and a four-year test with 1.35 μg/day, Kehoe concludes that after four or eight years, the blood level of the subjects would have risen to 80 µg/100 ml. The daily addition of 300 µg Pb to that of the diet did not raise the blood level after 420 days; within that test period, 12 mg of lead had not been re-excreted. Therefore, one calculates that 28 µg of lead are deposited in the body every day. From this experiment, Kehoe concludes that oral lead intake over a period of many years should not exceed 600 µg/day; he states that this dosage would result in the deposition of 8 mg lead per year (in a healthy man), and feels that such a rate of build-up could be tolerated for a lifetime without undue risk [43].

We must take into account that Kehoe's subjects were "healthy" and "normal", i.e., absorbed a maximum of 10% of the introduced lead. According to this, the tolerable limits would be approximately 60 µg Pb/day. People doing heavy physical labor with a correspondingly higher daily food intake have a comparatively lesser margin for additional lead intake from the air. Kehoe regards 8 mg of lead deposited within a year as safe; in 50 years, this would accrue to 400 mg. The release of 1% of this amount, i.e., 4 mg, would correspond to 40 mg lead taken orally for 10% absorption through the gastrointestinal tract.

Unfortunately, Kehoe's data are based on a very small sample. Moreover, activation of inactive lead stored in the skeleton is by no means certain. In this connection, it is noteworthy that, according to Eichler [18], the two American astronauts of Gemini V lost up to 15% of their bone calcium during the 8-day flight; the Russian cosmonaut and physician Jegorow also reported high Ca losses during the space flight. Whether such a rapid loss can occur under terrestrial conditions is questionable.

Investigations in occupational medicine offer another starting point for setting tolerance limits for lead stress:

In 1969, the following values were regarded as maximum work site concentrations (MAK):

West Germany	0,2	mg/m^3
Great Britain	0,15	mg/m^3
Yugoslavia	0.15	mg/m^3
Poland	0,05	mg/m^3
Czechoslovakia	0,05	mg/m^3
	0,25	mg/m^3 peak
U.S.S.R.	0,01	mg/m^3
Hungary	0,02	mg/m^3
U.S.A.	0,20	mg/m^3
	0,6	mg/m^3 peak

On the basis of many measurements of atmospheric lead concentrations, Mappes [62] tested the maximum permissible MAK in a battery factory, using aminolevulinic acid and coproporphyrin excretion in urine. He concluded that a maximum range of 150 - 200 µg Pb/m^3 is appropriate; work places with concentrations below 100 µg/m^3 had no significant effect on the functions investigated. He adds that ecological viewpoints were not considered in this study.

In a Japanese investigation of the same problem, Tsuchya and Harashima [90] arrived at the same conclusion; for a 40-hour week, they regard 0.12 mg/m^3 Pb or slightly higher as an appropriate TLV (threshold limit value), since above this the indicators point to lead stress.

We now need to calculate what lead content of the open atmosphere will correspond to a work site concentration of 100 µg/m^3.

First of all, we must point out that lead dust concentration at a work site is much higher than in the open air. As we discussed earlier, coarse particles do not penetrate to the lower air passages, and are only slightly significant because of (low) gastrointestinal tract absorption. In order to compare the lead content of the work site atmosphere with that of the open air, Mappes [61] divides it by a factor of 3. [Obviously, this is a crude tool indeed. It merely serves in considering the highly visible quantities of coarse dust (which are, however, of only slight biological significance) during rapid calculations on site. The factor can vary widely in either direction from case to case.] Accordingly, 100 µg Pb/m^3 of air at the work site has the same biological impact as 33 µg Pb/m^3 in the open air.

Furthermore, we shall consider that a person ventialtes 15 m^3 of air per day, 6 m^3 during the 8-hour work day, and 9 m^3 during the remaining 16 hours. In the course of a week, therefore, 5.6 = 30 m^3 of air, each containing 33 µg Pb = a total of 1000 µg of lead (rated as fine particles) are inhaled at the work site. For a non-lead worker, this quantity of 1000 µg lead dust would be prorated over 105 m^3 (as weekly ventilated volume). Thus, a lead concentration at the work site of average 100 µg/m^3 would correspond to an average lead content in the open of approximately 10 µg/m^3.

As discussed in Section 6.3.1., approximately 50 µg of lead are absorbed per day from an atmospheric concentration of 10 µg/m^3. Together with lead from the diet, this results in a lead intake of 80 µg/day, corresponding to an oral intake of 800 µg of lead alone.

Kehoe's limiting threshold of 600 µg lead per day for oral intake corresponds approximately to the limits given by calculating the safe lead concentration of the atmosphere at work sites. Even when other assumptions are made for calculating work site concentrations (e.g., a higher weighting of coarse dust) and higher values are derived, this would not contradict the threshold set by Kehoe, since Mappes clearly states that he ignored ecological considerations and did not have the opportunity to work with exposures lasting for decades.

Using this conversion of the MAK of 200 µg/m^3, this work site concentration would be equivalent to a lead content of the open air of 20 μg/m^3, as an average over a 7-day period. This results in a daily lead uptake of 100 μg, with an additional 30 μg from the diet. According to Kehoe's data, this quantity (in Kehoe's test, it was 127 μg orally absorbed from 1270 μg of lead) would lead after 8 years to a blood level of 80 μg/100 ml. It is likely that the constant lead stress for a worker at a work site with a MAK value of 200 μg/m^3 would also lead to a rise in lead deposition; Mappes, with his factor of 3 : 1 in comparing lead in the open air to lead in the work site atmosphere (for the same concentration because of the uneven grain spectrum) is therefore probably approximately correct.

On the grounds of the above considerations, unfortunately based on only very few investigations, we conclude with Kehoe that healthy individuals also should not absorb more than 60 μg/day. This threshold holds, even for healthy individuals, only as long as the lead deposit of 400 mg formed within 50 years does not become activated in later years, leading to toxic symptoms. Thirty μg/day are absorbed with the diet; the margin for sick individual is, therefore, very small.

In the subsequent discussion of thresholds, we will now refer to epidemiological studies.

6.3.6.3. Epidemiological studies on lead stress in the general population

Up to now there are no data on health damage due to lead in the atmosphere. It must be admitted, however, that at present it is scarcely possible to diagnose individual cases of this type, if they exist. Even if 1% of the population in areas with heavy traffic — a large number, in point of fact — were to seek out a physician because of symptoms listed for a slight case of lead poisoning, there is no chance that lead would be recognized as the cause: no tests for lead or an impaired porphyrin metabolism are run when a patient complains about fatigue, slight constipation, and other gastrointestinal symptoms. Even in clinics, such tests are not routine, and are ordered only in especially suspect cases. Series experiments would have to reach thousands of people in order to discover such isolated cases, although with such a large population sample, the number might be quite high.

Presently available studies on blood content, excretion of lead and ALA in the urine, and ALA-dehydratase activity in populations with varying lead exposures offer no uniform picture. Thomas et al. [88] found that men living near a freeway had 22.7 µg lead/100 ml blood; those living near the beach had 16.0 µg. In women, the ratio was 16.7 vs. 9.9 µg lead/100 ml blood. Horiuchi [33] reported similar values for inhabitants of Osaka: 24.9 µg/100 ml from inhabitants of heavy lead areas vs. 16.8 µg/100 ml for the control group.

Lob and Desbaumes [58] compared lead in blood and urine of adults in two facilities, one of which was near a freeway, the other in open country. For an average prison term of 15 - 16 months, no differences appeared in the blood; urine excretion, however, was 35.5 µg/*l* for inmates near the freeway vs. 28.8 µg/*l* for those in the country. This difference may not be due solely to the atmosphere; it might have been caused in part by, for instance, the diet, including vegetables raised in the garden of the facility.

Goldwater and Hoover [22] conclude from their study of the blood content and urine excretion of a total of 829 subjects from 16 states that their results did not vary essentially from those obtained for the past three decades. According to those measurements, there are also no clear-cut differences between rural and urban subjects. The aborigines in New Guinea had a blood level approximately the same as the population of industrial nations. It is, however, important to note that 95% of the sample had blood levels below 50 µg/100 ml, i.e., 5% were higher. These are easily overlooked in comparing averages which ranged mostly between 15 and 25 µg/100 ml; from the viewpoint of preventive medicine, though, they are significant. According to Horiuchi [33], 5 out of 63 healthy Japanese had a blood level above 50 µg/100 ml. Lehnert et al. [57] gives graphs of frequency distributions of blood levels in 400 lead-stress-free subjects, which indicate that only isolated individuals had more than 30 μg Pb/100 ml of blood; the average was 14.9 μg/100 ml.

In a later study by Lehnert et al. [55], garbage men in Frankfurt had blood levels of 23.5 μg/100 ml, and street cleaners — 28.7 μg. The delta-aminolavulinic acid (ALA) excretion in the urine in both groups revealed several isolated cases which the authors judged to be a biochemical indication of a danger point in the degree of poisoning. Schubert and Sangl [80], however, also working in Frankfurt a.M., found no increase in urinary ALA excretion for traffic policemen, policemen working in offices, and street cleaners, although 12 of the 127 traffic officers registered more than 50 μg Pb/100 ml in the blood. All groups had high average values for blood levels: traffic officers, 33 μg; office policemen, 30.1 μg; street cleaners, 29.1 μg Pb/100 ml blood. The authors did not test any rural groups.

Reichel et al. [72] found a remarkably high rise in blood levels after a three-hour exposure at an intersection. The rise from 12.2 to 26.2 μg Pb/100 ml blood (in traffic policemen),and from 15.1 to 23.0 μg Pb/100 ml(in ordinary subjects) was so great that it cannot even be approximated by intake from the air within 3 hours. The authors postulate activity of stored lead due to inhalation of leaded air. They performed no analyses on the possible diurnal periodicity of the blood lead content. A study of Haeger-Aronson et al. [26] on ALA-dehydratase activity in red blood cells of normal subjects, workers in city traffic and lead workers showed no significant differences between the normal subjects and those active in traffic. Hernberg and Nikkanen [29] had reported previously that ALA-D activity could be inhibited by blood levels below 20 μg.

Scanlon [77] found no significant difference between the blood levels in the umbilical cord of neonates from the center of Boston and those from the suburbs. The averages were 22.1 μg Pb/100 ml vs. 18.3 μg/100 ml. No measurements were taken of the blood levels in the mothers. Haas [24] obtained an average for the new-born of 14.98 μg/100 ml vs. 16.89 μg/100 ml for the mothers.

We have already discussed the formation of lead deposits in the body. Schroeder and Tipton [79] found 50 - 200 mg lead in the body, 91% of it in the bones; Barry and Mossman [3] — 250 mg in men above 60 years of age. Horiuchi [33] estimates the total lead in the body for adult Japanese to be over 100 mg; Kehoe [40], on the basis of his work in the U.S.A. — approximately 100 - 400 mg.

Some data on animals might be added to the studies on humans:

As noted, Smith et al. [83] and Lutmer et al. [60] let animals inhale air containing automobile exhaust gases. Within 4 years, an atmosphere of 2.5 $\mu g/m^3$ raised the lead deposits in the bones of rabbits by 64%, in guinea pigs — by 31%, over that of the control animals. The findings on the significantly higher lead content of the bones of pigeons from urban Philadelphia, compared to pigeons from a rural area [Tansy and Roth , 84], may not be due to air levels alone; possibilities for oral lead absorption from other sources might also be considerable for pigeons in a city.

The heavy metal poisoning observed in several animal species in a New York zoo is attributed to the high lead content of soils, grass, and foliage; it is said to derive from automobile exhaust gases [Bazell, 4]. This is the first mention of animal poisoning by lead from automobile exhaust gases. In their extensive literature survey of lead poisoning in animals, Richter and Schlatter [73] point out that no other cases have been described so far. Feeding cows with hay from freeway dividers raised the lead content of the milk and various organs, but led to no clinical symptoms of poisoning. Near lead smelters, lethal cases of lead poisoning in animals have occurred repeatedly up to the present time.

6.3.6.4. Assessment of danger to the health of the general population by lead intake; projected threshold tolerances

We base our determinations of threshold values for lead intake on the following assumptions:

1. A healthy human being ingests an average of 300 μg of lead daily with his diet, and absorbs 10%, i.e., 30 μg.

2. Inhaling air with a lead content of 1 $\mu g/m^3$ (in the form of aerosols from automobile exhaust gas) leads to an absorption of 5 μg/day, higher concentrations — correspondingly more. Due to the very different particle size, the lead concentration in the open air is biologically three times as significant as that of an equally high concentration at the work site of an individual.

3. A healthy person should not absorb more than 60 μg lead per day, so as not to raise the blood level. Limited excesses on isolated days or weeks are not important as long as they are interrupted by periods with lower lead intake. Absorption of an average of 130 μg lead/day would lead, even in healthy individuals, within 8 years to a blood level of 80 μg/100 ml, which approaches even occupational danger levels.

4. There are no grounds for concern that lead in the above dosages could lead to illnesses beyond the well-known symptoms of lead poisoning (particularly mutagenic or lessened-resistance effects, kidney damage, arteriosclerosis, carcinogenic effects, etc.).

5. Compared to the inorganic compounds, concentrations of organic lead compounds in the atmosphere are biologically insignificant.

6.3.7. Summary and conclusions

1. For lead, the interval between the amount absorbed unavoidably with the daily diet due to the natural lead content of soils, on the one hand, and that amount still tolerated by a healthy individual for decades, on the other, is much smaller than for other toxic substances (usually a ratio of 1 : 10; 1 : 2 — for lead).

2. Increased food intake, e.g., as by individuals performing heavy physical labor, a priori narrows the tolerance range. For patients with extended periods of increased enteral absorption or decreased lead excretion through the kidneys, the remaining safety margin between normal and maximally tolerable lead intake orally may already be too small.

3. Any additional lead stress in addition to the unavoidable intake from the diet, e.g., by lead in the atmosphere, is cause for concern when it affects the general population, including children and the sick, for periods of decades. Chronic stress due to lead in the atmosphere can be tolerated only if it is insignificant compared to the lead intake from the diet; this would be the case only for 10 - 15% of the amount absorbed orally, i.e., 3 - 4.5 μg/day.

4. A lead quantity of 4.5 μg is absorbed by inhaling air with an average content of 0.9 $\mu g/m^3$ Pb air for 24 hours. This maximal emission concentration may serve as a 7-day average. The short-term inhalation of higher concentrations (MIK short-term value) should not exceed 10 $\mu g/m^3$ Pb.

This threshold also removes the danger that lead intake could be increased significantly via contamination of plants or meat animals.

By way of comparison, we would like to offer the MIK values of several countries. These are not 7-day, but 24-hour averages:

Israel	5	µg Pb/m^3
Lead sulfide	3,5	µg Pb/m^3
Czechoslovakia	0,7	µg Pb/m^3, except for TEL
U.S.S.R.	0,7	µg Pb/m^3, except for TEL
U.S.A.	2,0	µg Pb/m^3 (threshold recommended by "State Air Preserver Board)

Limits projected by some states in the U.S.A.:

Massachusetts	5,0	µg/m^3
South Dakota	10,0	µg/m^3
California	1,2	µg/m^3

The assumptions used by us for determining MIK values need to be tested. The mere fact that no lead poisoning has been reported from areas with an atmospheric lead content of 2.5 µg/m^3 and above does not speak against the use of MIK values of 0.9 µg/m^3. We have already discussed the reasons for the great difficulties in diagnosing slight cases of lead poisoning. Apart from this, there are still many unsolved problems in lead absorption and excretion under various physiological and pathological conditions. Epidemiological studies of large population groups and of the sick would be most important; lead metabolism and enzymatic activity problems need to be resolved, as well as those of high blood levels (more than 50 µg/100 ml) in a small sector of the "normal" population, of the quantities of lead stored in the body and its activation, especially during pregnancy and in ages above 50 years.

Only after the numerous biological processes have been thoroughly researched will we be able to put the data on thresholds for lead stress in the general population on a solid scientific basis. The values given below can merely have a provisory character.

On the basis of the findings discussed above, we suggest the following values for lead:

MIK long-term (MIK_D):	0.001 mg/m^3
MIK short-term (MIK_K):	0.010 mg/m^3

with a maximal excess of up to 0.20 mg/m^3 for 90 seconds.

6.4 Oxidants

6.4.1 Preliminary comments

While CO, NO, the lead compounds, and a large part of the hydrocarbons are direct components, i. e., primary products, of the vehicle exhaust gas, the "oxidants" and some other compounds which are formed with them are secondary products which arise from auto exhaust emissions only in the atmosphere, particularly with intense solar radiation. Out of this complex of substances which are of secondary occurrence, the group of the oxidants is of particular interest because the severe action of these materials in irritating the mucous membranes and their strong odor has produced considerable stress on the population in the regions affected by "photochemical smog". The oxidants also have a distinct phytotoxic effect which causes increasingly greater economic damage through loss of yield and reduction of quality.

Of this group of compounds, only the principal components such as ozone, peroxyacetyl nitrate (PAN) and similar peroxyacetyl compounds, and some alkyl hydroperoxides have been identified satisfactorily. Many of the products, such as ozonides and organic radicals,are so unstable that they evade specific analysis. But it is just such compounds which are strong irritants because of their aggressive nature, and are therefore of interest in air hygiene.

As appears from the designation as oxidants, these materials have strong oxidizing power. This property makes a common analytical determination of the whole group of compounds possible [1]. The bulk determination of the oxidants, to be sure, has all the disadvantages which are common to relatively unspecific total determinations. The results obtained are only approximations, requiring added correction factors.

Thus, all those irritants which have no oxidizing properties are not determined. Furthermore, NO_2, which is always present in photochemical reactions, simulates excessively high values because of its strong oxidizing power. SO_2, by contrast, is a reducing agent, and will compensate for part of the oxidizing effect, giving a value which is too low.

This cross-sensitivity of the method to two of the air pollutants which occur most frequently greatly limits the evidential value of the usual methods for determining oxidants unless one performs parallel analyses for NO_2 and SO_2, thus determining the correction factors.

6.4.2 Theories of origin

The principal prerequisite for the formation of a "photochemical smog" is the simultaneous presence of nitrogen oxides (NO_x) and reactive hydrocarbons, which are activated by long-wave ultraviolet light (320-400 nm). The initial step of the photochemical reaction is the photolysis of NO_2 by the action of sunlight, liberating atomic oxygen:

$$NO_2 \xrightarrow{h.\nu} NO + O^{\bullet}$$

This then reacts further with the other components in the air, for example (Wagner, [26]):

(2) $O + O_2 \text{ ——— } O_3$

(3) $O_3 + NO \text{ ——— } O_2 + \underline{NO_2}$

(4) $O + RH \text{ ——— } R^{\bullet} + RCHO$

(5) $R^{\bullet} + O_2 \text{ ——— } RO_2^{\bullet}$

(6) $\mathrm{RO_2\bullet} + \mathrm{NO} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{RO^\bullet} + \underline{\mathrm{NO_2}}$

(7) $\mathrm{RO^\bullet} + \underline{\mathrm{NO_2}} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{R{-}O{-}NO_2}$

(8) $\mathrm{O_3} - \mathrm{RH} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{RCHO{+}RCO_2\bullet}$

(9) $\mathrm{RCO_2\bullet} + \mathrm{NO} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{RCO^\bullet} + \underline{\mathrm{NO_2}}$

(10) $\mathrm{RCO^\bullet} + \mathrm{O_2} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{RCO_3\bullet}$

(11) $\mathrm{RCO_3\bullet} + \underline{\mathrm{NO_2}} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{RCO_3NO_2}$

(12) $\mathrm{R^\bullet} + \underline{\mathrm{NO_2}} \;\rule[0.5ex]{4em}{0.4pt}\; \mathrm{RNO_2}$

The entire reaction is catalyzed by a series of hydrocarbons, primarily olefins and substituted aromatics. Labile intermediate compounds such as ozonides, peroxides and organic radicals form. They, in turn, react further and introduce a chain reaction.

The sum of the reaction steps gives a characteristic concentration curve, which can be represented in a scheme using 4 reaction components (Figure 1).

The NO originally present is converted into NO_2 by the O_2 content of the air. The presence of the hydrocarbons catalyzes this reaction, which normally goes very slowly. As soon as the highest NO_2 concentration is reached, oxidant formation begins, with simultaneously accelerated consumption of hydrocarbons. This experimentally determined reaction course explains why the concentration peaks of the individual reaction components in the outside air are displaced from each other. Figure 2 shows a schematic representation of the daily concentration curves of some important automobile exhaust gas components, to clarify the peak shift from the photochemical reaction (Wagner, [26]).

While CO, NO and the hydrocarbon concentration curves correspond strictly to the traffic situation, the NO_2 peak appears only with a delay. The oxidant peak appears even

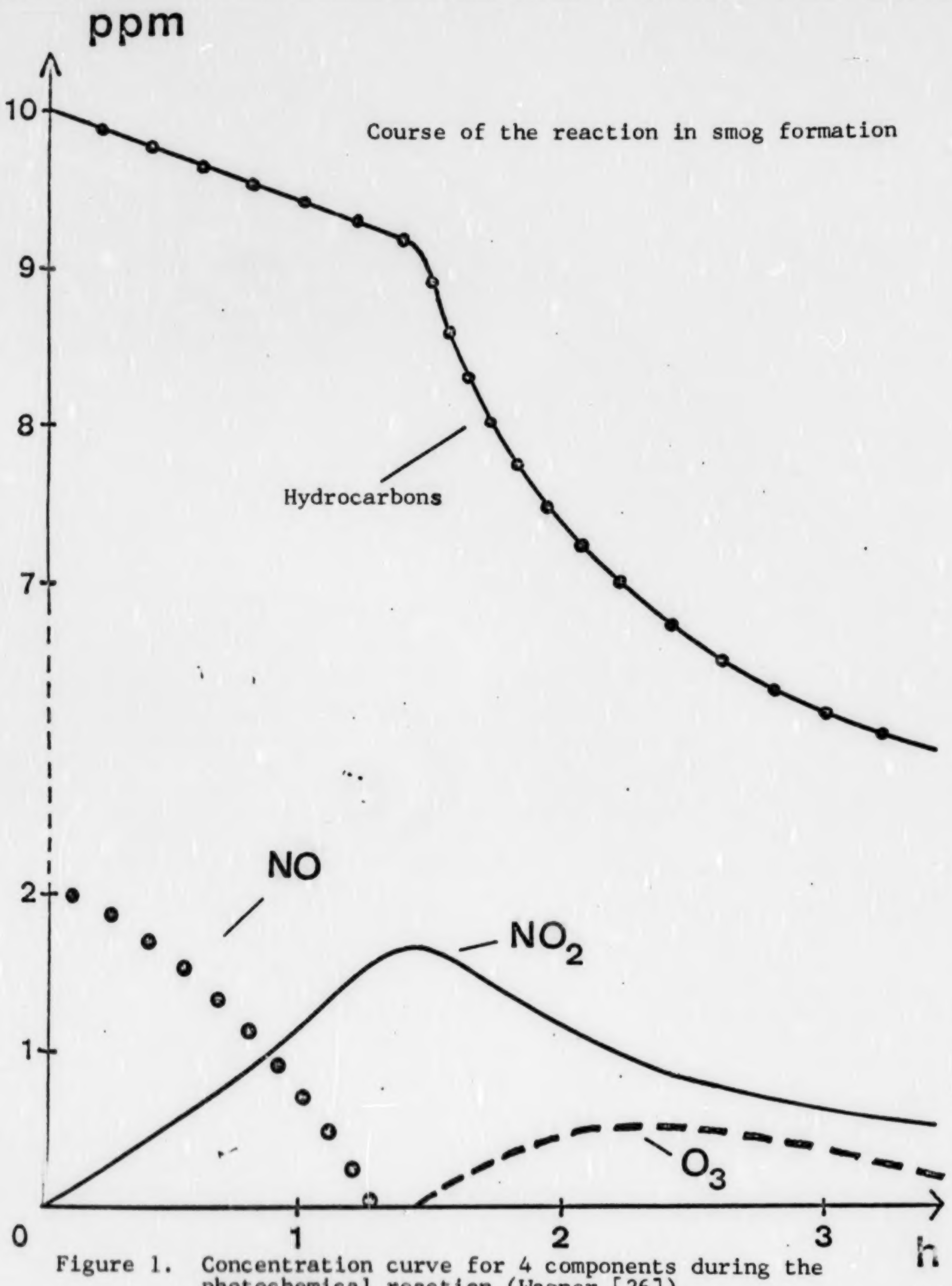


Figure 1. Concentration curve for 4 components during the photochemical reaction (Wagner [26]).

later. The solar radiation is at its maximum at this time. No oxidant peak and only a very slight NO_2 peak forms in the evening, because the solar radiation needed for the photochemical reaction is no longer strong enough.

The apparent contradiction which arises from the reaction curve and the individual steps can be explained as follows:

The appearance of significant O_3 concentrations is possible only if NO has decreased to a minimum, because NO always reacts immediately with ozone (forming NO_2 and O_2). In other words, as long as NO is present in excess it immediately traps the ozone which appears. High NO concentrations, then, cannot coincide with high O_3 concentrations, as the high affinity of these two materials excludes it. Only when NO has largely been oxidized to NO_2 can we consider the appearance of O_3. This is one reason why measurements during the highest traffic density always measure very low O_3 values.

Another paradox is the fact that NO_2, the compound which is photolytically destroyed by the light and which starts the photochemical action, increases continuously, at least during the first phase of the photochemical reaction. This is due to the fact that in addition to atomic oxygen and its addition compound with the oxygen of the air, ozone, highly reactive oxidized hydrocarbon compounds also continuously reoxidize the NO formed back to NO_2.

The sum of all these competing reactions then appears in the concentration curves shown in Figure 2.

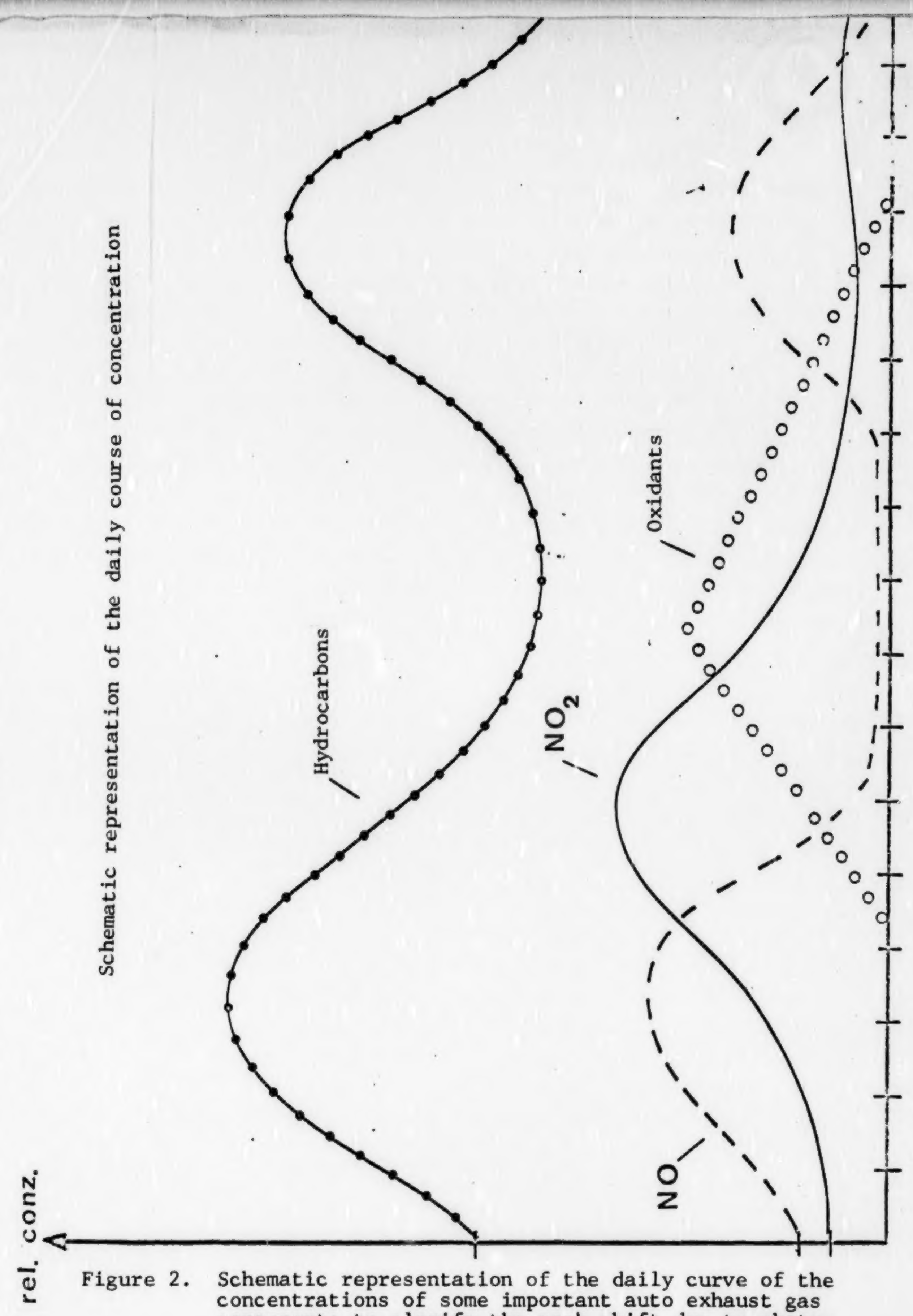


Figure 2. Schematic representation of the daily curve of the concentrations of some important auto exhaust gas components to clarify the peak shift due to photochemical reactions (Wagner [26]).

Various parameters can be used to quantify the photochemical smog phenomenon: the formation rate of NO_2, of ozone, peroxyacetyl nitrate (PAN), formaldehyde, or the intensity of its effect, such as reduction in visibility (aerosol formation), the phytotoxicity or the eye irritation. Although these phenomena are partially dependent on each other, their appearance varies, depending on the nature of the hydrocarbon-NO_x mixture.

For instance, the photochemical activity measured by the rate of NO_2 formation need not agree at all with the eye irritation or the oxidant formation.

6.4.3 Effects.

The products of photochemical smog, including the pure oxidants, have an extremely strong irritant effect on the mucous and conjunctival membranes, so that this form of air pollution, the "photochemical smog" is one of the most unpleasant forms of air pollution.

As results of direct action, we can consider:

1. Eye irritation and irritation of the upper respiratory tract.
2. Damage to the lung function (increase of the respiratory tract resistance, reduction of the vital capacity and of the expiration volume).
3. Danger to previously damaged persons, increase in the frequency of attacks (asthmatics, chronic bronchitics).
4. Reduction of capability.
5. Stress (unspecific).
6. Weakening of the ultraviolet portion of the sunlight (reduced Vitamin D formation).

There are also indirect effects: reduction in visibility and odor stress can produce injury to well-being through psychic factors (also stress-producing).

The main component of the pure oxidants is ozone. It makes up 90% of the total oxidants.

Many of the criteria were, therefore, determined in model experiments with ozone. But the ozone action by no means explains all the irritation and damage phenomena. For instance, it has only very slight effect on generating tears. Therefore, more and more experiments were done with irradiated exhaust gases and with direct atmospheric "smog", even though a satisfactory assignment of cause and effect is much more difficult in these cases because of the uncontrollable experimental conditions.

The following table shows the limiting concentrations for a biological effect from the action of ozone or total oxidants on man (Los Angeles smog or irradiated automobile exhaust gases) (Table based on [2]).

Concentrations ppm	 mg/m^3	Components	Duration of action	Effect
0.02	40	O_3	--	odor threshold
0.1	200	photochemical smog		eye irritation
0.13	250	"	maximum daily concentration	aggravation of problems for asthmatics (increase in frequency of attacks).
0.03-0.3	60-590	"	1 hour	reduction of capacity in athletes, reduced vital capacity
0.08		O_3	3 hours	23% increase in mortality after Streptococcus pneumonia
0.3	590	O_3	continuous during the working day	irritation of mucous membranes of the upper respiratory tract
0.5	980	O_3	3 hrs/day, 6 days per week after 8 weeks	change in lung function (reduced expiration volume)
0.60-0.80	1180 1570	O_3	2 hrs.	diffusion injury, damage to the diffusion capacity of lung (DL_{CO})
0.1-1.0	200 1960	O_3	1 - 1.5 hours	increase in respiratory resistance, irritation to cough, fatigue
1.3		O_3	3 hours	significant increase in mortality after Klebsiella pneumonia
9.0	17600	O_3		acute lung edema (in occupational exposure)
[illegible].2		O_3	17 weeks	60% increase in mortality from Mycobacterium tuberculosis inf.
2.5		O_3	5 weeks	epithelreduplications, lung adenomas

6.4.3.1 Eye irritation

Eye irritation is the best-known phenomenon. It is used for quantitative determination of the oxidant action of photochemical mixtures (Wayne, [3]). There are 3 criteria:

1. strength of the irritation ("severity index")
2. time to the first indication of irritation ("response delay index")
3. percentage susceptibility of test subjects ("quantal index").

There is a direct relation between the strength of the irritation (SI) from a reaction mixture and the time to the appearance of the irritation (RDI).

The correlation between eye irritation and oxidant concentration is highly significant (Richardson and Middelton [4, 5])(Figure 3).

The composition of an irradiated reaction mixture is of decisive importance for the irritant effect. For instance, as a rule, irradiated NO_x-olefin mixtures have a far stronger irritant action on mucous membranes than mixtures of NO_x and aromatics.

To be sure, irradiated automobile exhaust gases from olefinic and aromatic fuels are almost identical in their eye irritation because the original composition is completely changed by the combustion in the engine.

In experiments with individual olefin-NO_x mixtures, maximum eye irritation appeared at a ratio of 0.5 - 2 ppm NO_x to 1 - 3 ppm olefins (Schuck et al. [6]). With irradiated automobile exhaust gases, this "optimum" was at 1 ppm NO_x to 12 ppm total hydrocarbons. This is important for evaluation of the general situation (Korth et al. [7])(Figure 4).

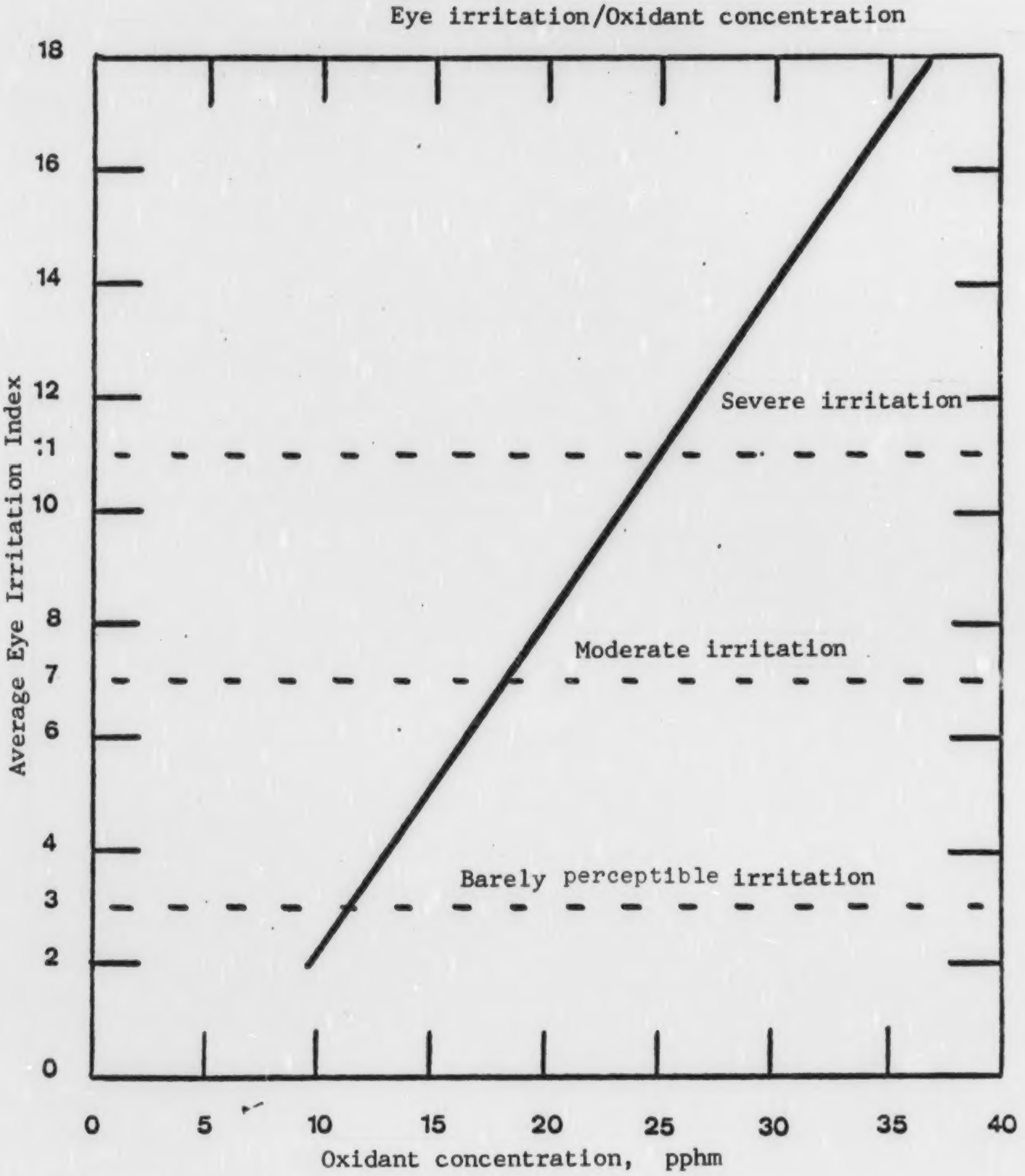


Figure 3. Eye irritation of "Los Angeles smog" as a function of oxidant concentration. Based on Richardson and Middelton [4, 5].

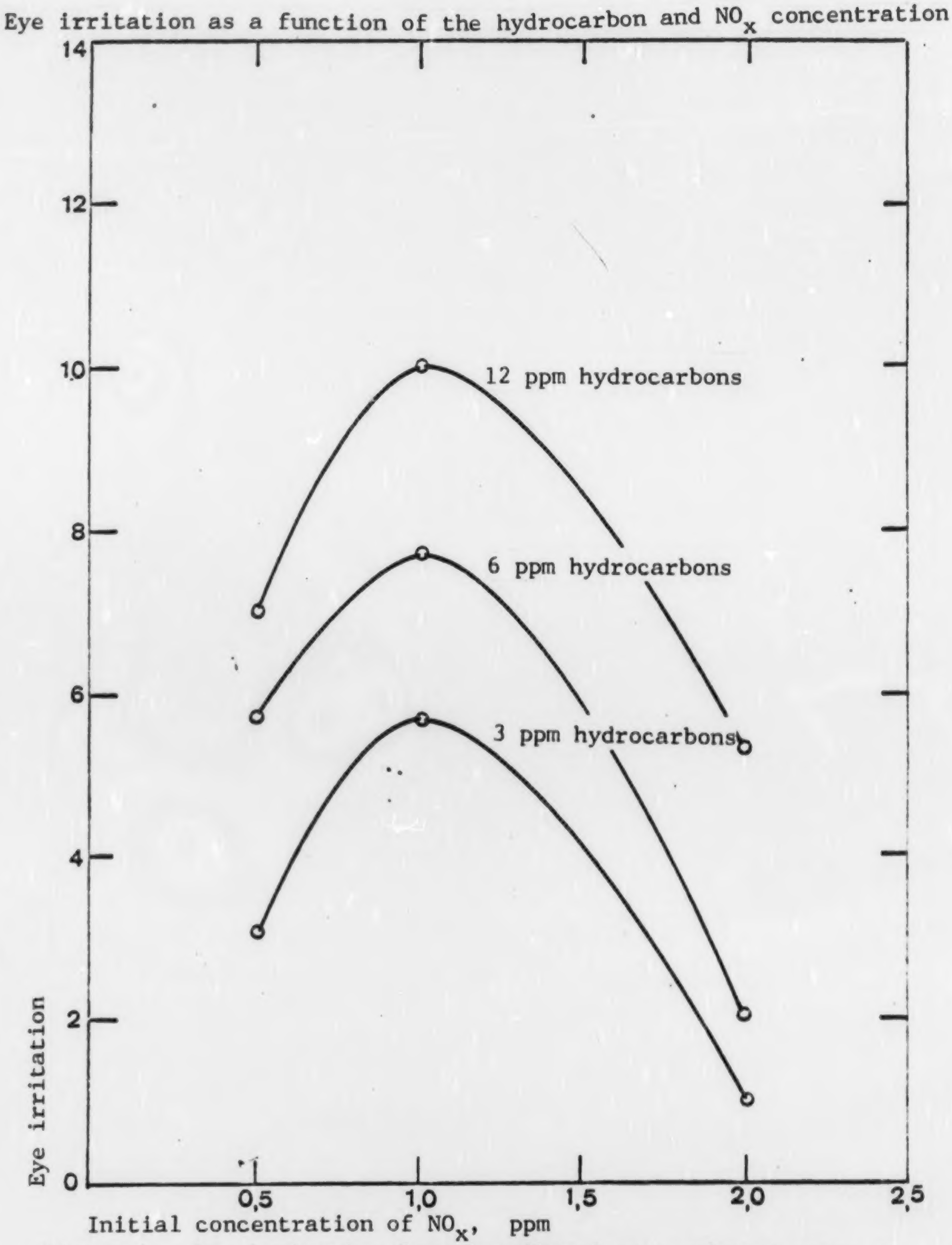


Figure 4. Eye irritation from irradiated auto exhaust gases as a function of hydrocarbon and NO_x concentrations. According to Korth et al. [7].

6.4.3.2 Increased frequency of attacks in asthmatics

In a three-month study in Los Angeles with 137 asthmatics, a significant increase in the frequency of attacks appeared if the oxidant concentration rose above 0.13 ppm during the smog periods. The attacks occurred with a time delay of several hours. Six percent of the asthmatics showed this reaction at a concentration of only 0.1 ppm. This must be considered in establishing limiting values (Schoettlin and Landau [8]).

6.4.3.3 Reduction of capacity in athletes

A distinct reduction of capacity in athletes during natural photochemical smog episodes was established. Several other factors were also considered (NO_x, relative humidity, temperature, wind velocity and direction) but they did not correlate with the phenomena observed (Wayne et al. [9])(Figure 5).

6.4.3.4 Diffusion disturbances

The CO diffusion capacity (DL_{CO}) of test subjects decreased distinctly after inhalation of 0.6-0.8 ppm ozone during 2 hours. The authors ascribed this effect to a lengthening of the alveolo-capillary diffusion path by about 50%. The short recovery time allowed conjecture of a pure edema formation (Young et al. [10].

6.4.3.5 Change of the respiratory tract resistance

Measurements of the flow resistance in the respiratory tract by means of whole body plethysmography gave a distinct increase in the resistance for all 4 test subjects even at one-hour inhalation of 0.1, 0.4, 0.6 and 1.0 ppm ozone. Normalization of the value occurred only some hours after the

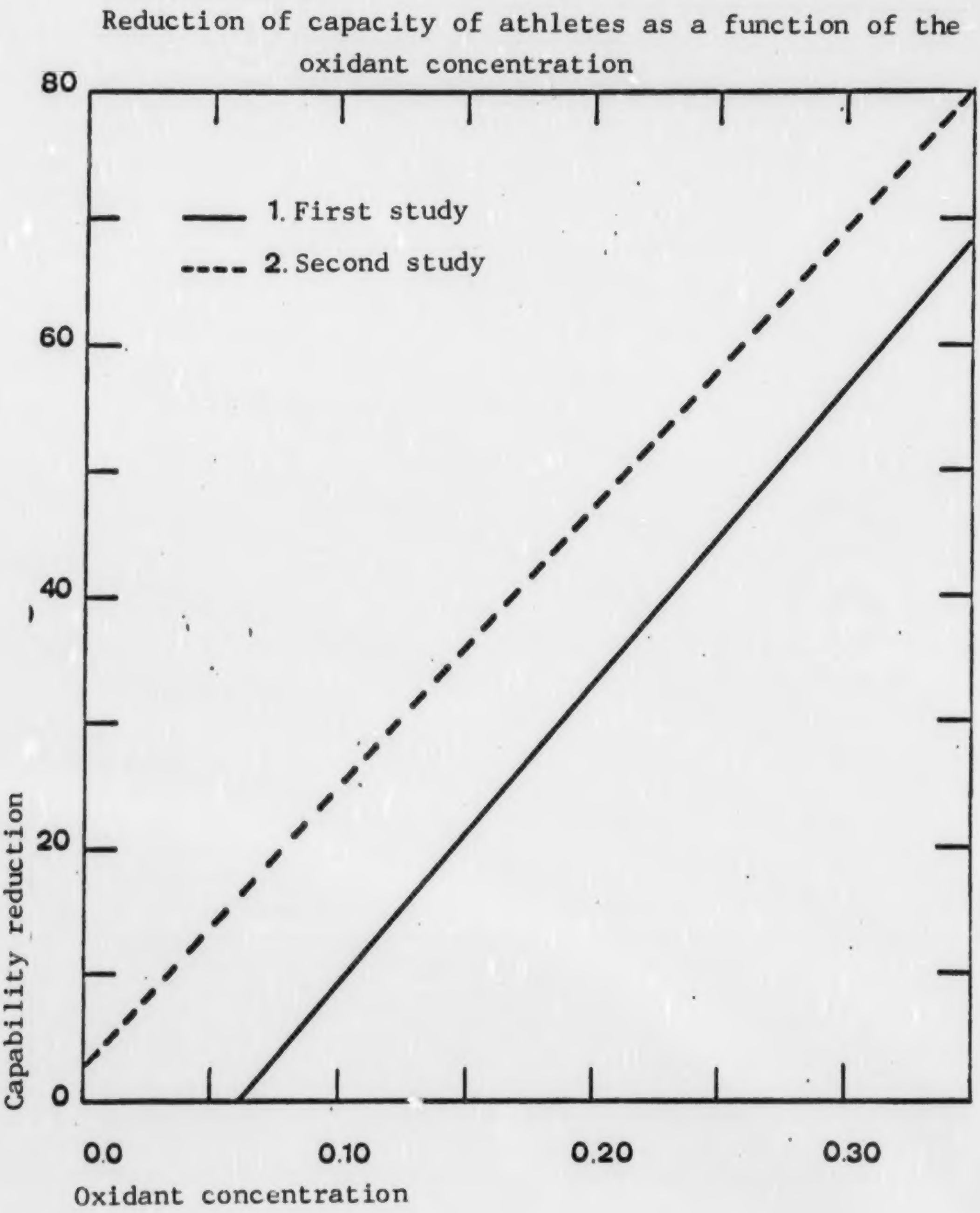


Figure 5. Effect of natural photochemical smog on the capacity of athletes. According to Wayne et al. [9].

end of the exposure. Irradiated automobile exhaust gases produced the same effect in the animal experiment. Here, reaction mixtures with an oxidant content of 0.33 - 0.35 ppm led to an increase of the respiratory tract resistance by more than 100% (Goldsmith and Nadel [11])(Figure 6).

6.4.3.6 Other effects

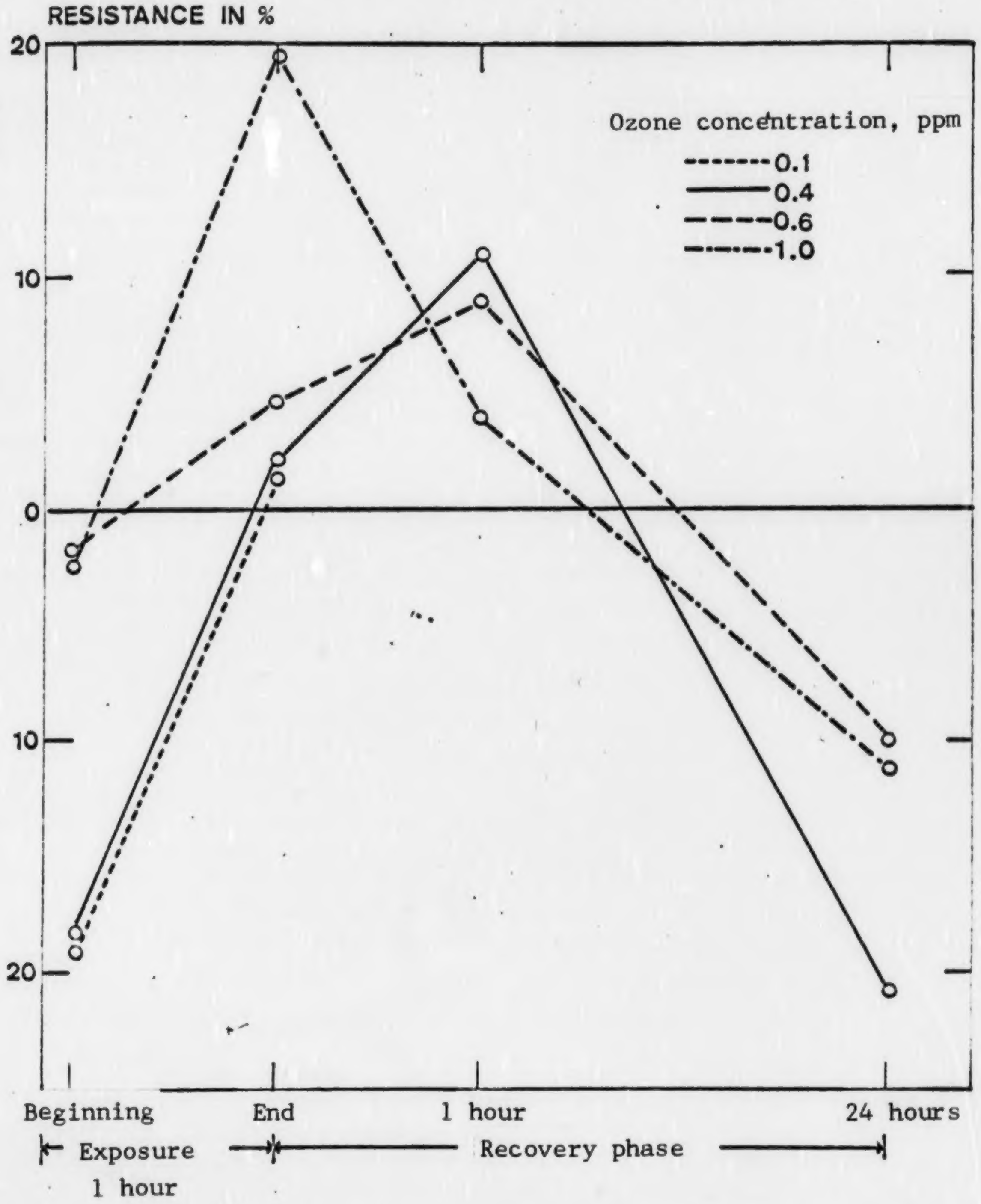
Four other reference points for possible effects appeared from findings in animal experiments:

Susceptibility to infectious germs

In animal experiments, increased susceptibility of animals stressed with ozone or irradiated vehicle exhaust gases to pathogenic germs was established. In part, the streptococci and Klebsiella pneumoniae which were used led to 23% increase in mortality at an ozone concentration of 0.08 ppm (for 3 hours) as compared to control animals which received only bacterial aerosols. Automobile exhaust gases with an oxidant content of 0.35 to 0.67 ppm also led to a decrease in resistance (Coffin et al. [12]; Coffin and Blommer [13]).

Aging

Experiments with guinea pigs, rabbits and mice have shown that ozone promotes the cross-linking of collagen and elastin fibers and, therefore, the aging of connective tissue in the lungs. In their total development, also, the animals with regular stress from ozone (1 hour per week for one year) showed premature aging phenomena (Stokinger [14]; Buell et al. [15]). As the structure of the connective tissue (elastin/collagen) in the human lung does not differ from that in the animal species studied, one can assume that the same reactions will occur in the human lung.



Effect of ozone on the respiratory tract resistance

Figure 6. Change in the respiratory tract resistance under the influence of ozone. According to Goldsmith et al.[11].

Stress

It appears from studies on guinea pigs and mice that an unspecific stress reaction is initiated by natural photochemical smog and by irradiated automobile exhaust gases. Other study results from experiments with artificial photochemical smog (irradiated automobile exhaust gas) on larger sets of experimental animals indicate the possibility of disturbances to fertility, increase in the number of stillbirths and deformations (Hueter et al [16]; Lewis et al. [17]).

Indirect effect (aerosol formation, visibility reduction)

Visibility reduction from aerosol formation is a side effect of the photochemical reaction which can injure human well-being on one hand through psychogenic factors, and on the other hand through weakening of the ultraviolet radiation. The aerosol formation is directly proportional to the oxidant concentration (Groblicki and Nebel [18]).

The simultaneous presence of SO_2 in the NO_x-hydrocarbon system plays a large part here. Certain hydrocarbons also form them as a result of the photochemical reaction. This tendency depends on the structure of the hydrocarbon. The higher olefins are particularly effective (Goetz and Pueschel [19]; Stevenson [20]).

If an aerosol is already present, then other hydrocarbons which do not themselves exhibit aerosol formation can contribute to further aerosol development.

Relative tendency of hydrocarbons toward aerosol formation in the presence of SO_2 and NO_x, with irradiation:

2-methylpentane	(0)
n-butane	(0.1)
ethylene	(2.2)
1-butene	(2.85)
2-butene	(3.0)
2-pentene	(3.0)
2-hexene	(3.05)
1-hexene	(3.35)
3-heptene	(3.55)

Aromatics and paraffins combined with nitrogen oxides show little or no tendency for aerosol formation on irradiation.

As relations between aerosol formation and concentrations of the components, we have the following (Schuck and Doyle [21]; Reckner et al. [22]):

1. Aerosol formation increases with increasing SO_2 concentration. (The formation rate decreases slowly with higher SO_2 concentrations).
2. The aerosol formation also increases with an increasing proportion of hydrocarbons (up to an optimum).
3. The aerosol formation increases with increasing NO_x content (up to an optimum).

An analysis of the aerosols derived from the system SO_2-NO_x-hydrocarbon showed that it was primarily a sulfuric acid aerosol: 40% S, 1% C. As the aerosol formation occurs only after high to maximal NO_2 concentrations are reached and runs parallel with the PAN formation, a decisive role for these components is probable in the oxidation of SO_2 to SO_x. Automobile exhaust gases can give strong aerosol formation on irradiation, even without the presence of SO_2. Automobile exhaust gases derived from olefinic fuels give particularly strong aerosol formation. Exhaust gases from combustion of paraffinic and aromatic fuels show only slight tendencies in this respect. Engine conditions which lead to a high content of unburned hydrocarbons in the exhaust promote the aerosol formation (Schuck et al. [23]). Here, the aerosols have a different composition than those mentioned above, which were formed in the presence of SO_2: 34% C, 5.3% H, 1.8% N (Renzetti and Doyle [24]) Different types of photochemically caused aerosol formation occur, then, depending on the basic load in a region.

Effect on material

Oxidants, because of their aggressiveness, also attack materials. Plastics which contain C-C double bonds in their structure, such as synthetic rubber, are particularly extremely sensitive to ozone. But even textiles and dyes are destroyed. Hairline cracks appear in automobile tires, insulating materials, and plastic objects, making them useless. The destructive action on this type of compounds goes so rapidly and is so proportional to the pollutant concentration that one semi-quantitative method for ozone determination, the "rubber cracking" method, is based on it.

Phytotoxicity

Plant damage in the Los Angeles area provided the first indications of a new specific form of air pollution with a characteristic pattern of action in the early 1940's. By 1950, this phenomenon, which had been local, had spread over a large part of southern California and the region around San Francisco. It was finally observed in other regions of the USA. It led to increasing financial losses through reduction in yield of fruits, vegetables and ornamental plants. In some plants the type of damage is so characteristic that one can use it as a biological indicator for oxidants. Tobacco is particularly suitable in this respect (Heck et al. [25]). Although these plant damages are an important economic factor, the phytotoxicity is less important than the effect of this group of compounds on humans.

6.4.4 Summary and conclusions

The evolution of the composition of the atmospheric pollutants in northern Europe in recent years is undoubtedly taking an unfavorable course. The total emissions of NO_x and hydrocarbons have risen steadily, continuously promoting the tendency for photochemical smog formation. The following regularities determine the course of the photochemical reaction and, with it, the formation of oxidants:

1. The reaction is directly proportional to the intensity of the light.
2. The reaction is proportional (not directly) to the concentrations of NO_x and hydrocarbons.
3. The reaction depends on the ratio of NO_x to hydrocarbons. In general, the reaction increases with increasing hydrocarbon content (until an optimum is reached).
4. The reaction is also sensitized by certain organic compounds. Then it proceeds at wavelengths which otherwise produce no photochemical reaction.

In addition, temperature, humidity, and air pollutants such as SO_2 and CO which are simultaneously present affect the total course of the reaction.

As the light intensity and temperature have a decisive effect on the total course of the photochemical reaction, we can estimate that with the conditions at our latitude, the extreme stresses and economic damages from oxidants will not occur to the extent that they do in Los Angeles. This is only a difference in degree, however.

As a series of other factors, such as concentration of the reactants, reactant ratio, and sensitization affect the photochemical reaction, some of the positive factors can be cancelled by others.

As the presence of hydrocarbons and nitrogen oxides is a prerequisite for the reaction, the height of the atmospheric oxidant content can be controlled by establishing suitable limits for hydrocarbons so that the prescribed limiting concentrations for oxidants is ensured. Although the quantitative relation between hydrocarbon concentrations and oxidant concentrations can not yet be considered as explained through laboratory experiments with ultraviolet irradiation of reactive hydrocarbons, and ability to transfer laboratory findings to the atmospheric load situation is affected by large errors because of meteorological factors, we can, from the existing atmospheric measurements of hydrocarbons on one hand, and from corresponding oxidants on the other hand, derive certain quantitative relations between the two quantities.

Figures 7 and 8 show the relations measured in various cities of the USA between morning hydrocarbon concentrations (including methane) and the maximum oxidant concentration (5 minute peak) measured on the same day. From the relations shown we can determine that hydrocarbon concentrations of 2.5 ppm allow us to expect a maximum oxidant concentration of 0.10 ppm, while maintenance of a hydrocarbon concentration of 4 ppm

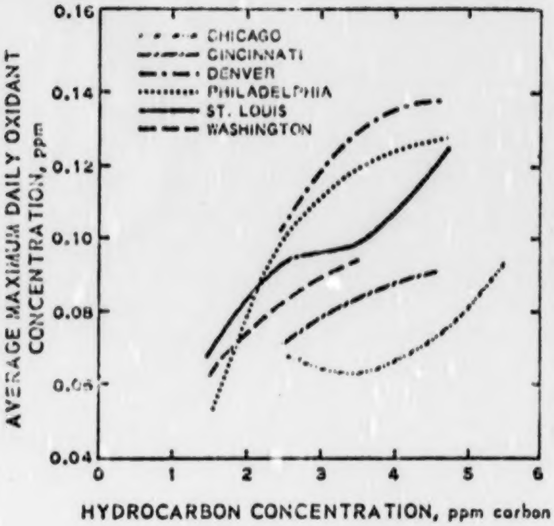


Figure 7. Effect of the morning hydrocarbon concentrations measured between 6:00 and 9:00 on the maximum oxidant concentration measured on the same day in the months of June, July and August 1965-1967 [2].

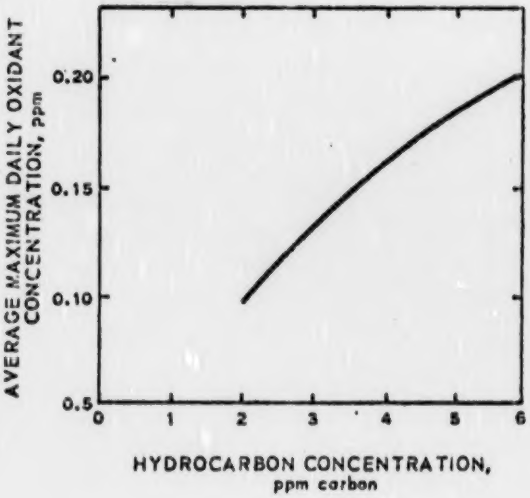


Figure 8. Effect of the morning hydrocarbon concentrations measured between 6:00 and 9:00 on the oxidant concentration measured on the same day in Los Angeles during the months of April to September 1962 and 1963 [2].

leads us to expect no higher oxidant concentrations than a maximum of 0.15 ppm.

According to the existing effect criteria, the recommended limits recommended for oxidants are:

Maximum immission concentration (long term) (MIK_D) 0.05 ppm.
Maximum immission concentration (short term)(MIK_K) 0.15 ppm.

But we must expressly mention that these limits are established from American measurements. As there are no comparable measurements in the Federal Republic, it seemed reasonable to us to take the atmospheric conditions mentioned here as also valid for us.

REFERENCES

(Section 6.1, Carbon Monoxide)

1. Air Quality Criteria for Carbon Monoxide. Washington, U.S. Department of Health, Education, and Welfare, 1970.

2. Materialien zum Umweltprogramm der Bundesregierung, 1971 (Materials on the Environmental Program of the Federal Government). Published by the Federal Minister of the Interior. Separate Appendix to 6th German Federal Election Report VI/2710.

3 Reine Luft für morgen. Utopie oder Wirklichkeit? Ein Konzept f. d. Land NRW bis 1980 (Pure Air Tomorrow? Utopia or Reality? A Concept for the State of North Rhine-Westfalia up to 1980). Published by the Minister for Labor. Health, and Social Welfare of the State of North Rhine-Westfalia, Dortmund, Westphalia, 1972.

4. Fodor, G. G. Carbon Oxides Medical Institute for Air Hygiene and Silicosis Research Annual Report, 1967/68. Based on: Enger (1969)48.

5. Fodor, G. G. and G. Winneke. Effect of Low Concentrations on Resistance to Monotony and on Psychomotor Capacity. Staub, Vol. 32, 1972, pp. 46-54.

6. Fodor, G. G., G. Malorny and H..J. Colmant. On the Effect of the Electroencephalogram of the Albino Rat after Unilateral Carotid Ligature and Subsequent CO Poisoning. Naunyn-Schmeidebergs Arch. exp. Parh. Pharm., Vol. 249, 1964, pp. 215-224.

7. Schlipköter, H.-W. On the Effect of Carbon Monoxide. VDI-Presseinformation, No. 33, 1971.

8. Goldsmith, J. R. and S. A. Landaw. Carbon Monoxide and Human Health. Science, Vol. 162, 1968, pp. 1352-1359.

9. Peterson, J. E. and R. D. Stewart. Absorption and Elimination of Carbon Monoxide by Inactive Young Men. Arch. Environ. Health, Vol. 21, 1970, pp. 165-171.

10. Fodor, G. G. Carbon Monoxide as an Imission Component of Automobile Exhaust Gases. Medical Institute for Air Hygiene and Silicosis Research, Annual Report, 1970. Dusseldorf, Triltsch, 1971, pp. 58-62

11. Forbes, W. H., F. Sargent and F. J. W. Roughton. The Rate of Carbon Monoxide Intake by Normal Men. Amer. J. Physiol., Vol. 143, 1945, pp. 594-608.

12. Coburn, R. F., R. E. Forster and P. B. Kane. Consideration of the Physiology and Variables that Determine the Blood Carboxyhemoglobin Concentration in Man. J. Clin. Invest., Vol. 41, 1965, pp. 1899-1910.

13. Knelson, J. H. Addendum. Carbon Monoxide Colloquium of the Society of German Engineers, Lecture, October 28 - 29, 1971, Dusseldorf.

14. Coburn, R. F. Biological Effects of Carbon Monoxide. Ann. New York Acad. of Science, Vol. 174, 1970, p. 11.

15. Borbely, F. On the Existence of Chronic Carbon Monoxide Poisoning. Internist, Vol. 2, 1961, pp. 265-269.

16. Schlipkoter, H.-W. Concluding Remarks. Staub-Reinhaltung der Luft, Vol. 32, 1972, pp. 72-73.

17. McFarland, R. A., F. J. Roughton, M. H. Haperin and J. J. Niven. The Effects of Carbon Monoxide and Altitude on Visual Thresholds. Aviation Med., Vol. 15, 1944, pp. 381-394.

18. Halperin, M. H. et al. The Time Course of the Effects of Carbon Monoxide on Visual Thresholds. J. Physiol., Vol. 146, 1959, pp. 583-593.

19. Beard, R. R. and G. A. Wertheim. Behavioral Impairment Associated with Small Doses of Carbon Monoxide. Amer. J. Public Health, Vol. 57, November, 1967, pp. 2012-2011.

20. Beard, R. R. and N. Grandstaff. CO Exposure and Cerebral Function. Paper Presented at the New York Academy of Sciences, Conference on Biological Effects of Carbon Monoxide. New York City, January 12 - 14, 1970.

21. Horvath, S. F. James, J. F. Hanlon and Th. E. Dahms. Carbon Monoxide and Vigilance. Potential Danger from Existing Urban Concentrations. In: Project Clear Air, Vol. 2. University of California (at Santa Barbara) Res. Proj. 5-4, 11 pp., 1970, p. 1.

22. Groll-Knapp, E., H. Wagner, H. Hauck and M. Haider. Effects of Small Carbon Monoxide Concentrations on Vigilance and Computer-Analyzed Brain Potentials. VDI-Bericht, No. 180, 1972, pp. 101-104.

23. Stewart, R. D. et al. Experimental Human Exposure to Carbon Monoxide. Reported under Contract CRC-APRAC. Project No. CAPM-3-68. Coordinating Research Council, Inc., 1969.

24. Mikulka, P. et al. The Effect of Carbon Monoxide on Human Performance. Paper presented at the Fifth Annual Conference on Atmospheric Contamination in Confined Spaces, Air Force Aerospace Medical Research Laboratory. Wright-Patterson Air Force Base, Dayton, Ohio, 1969.

25. Forbes, W. H. et al. The Influence of Moderate Carbon Monoxide Poisoning Upon the Ability to Drive Automobiles. J. Ind. Hyg. Toxicol., Vol. 19, 1937, pp. 598 - 603.

26. Ray, A. M. and T. H. Rockwell. An Exploratory Study of Automobile Driving Performance Under the Influence of Low Levels of Carboxyhemoglobin. Ohio State University, Department of Industrial Engineering, Report No. IE-1, Columbus, August, 1967.

27. Grudzinska, B. Electroencephalogic Patterns in Cases of Chronic Exposure to Carbon Monoxide in Air. Folia Med. Cracov., Vol. 5, 1963, pp. 493 - 515.

28. Bender, W., M. Goethert and G. Malorny. The Effect of Low Carbon Monoxide Concentrations on Psychological Functions. VDI-Berichte, No. 180, 1972, pp. 91-95.

29. Schulte, J. H. Effects of Mild Carbon Monoxide Intoxication. Arch. Environ. Health., Vol. 7, 1963, pp. 524-530.

30. Ayres, S. M., S. Gianelli, Jr., and R. G. Armstrong Carboxyhemoglobin: Hemodynamic and Respiratory Responses to Small Concentrations. Science, Vol. 149, 1965, pp. 193-194.

31. Ayres, S. M. et al. Systemic and Myocardial Hemodynamic Responses to Relatively Small Concentrations of Carboxyhemoglobin (COHB). Arch. Environ. Health, Vol. 18, 1969, pp. 699-709.

32. Knelson, J. H. Air Quality Criteria and Imission Limiting Values for Carbon Monoxide in the United States. VDI-Berichte, No. 180, 1972, pp. 96-99.

33. Brody, J. S. and R. F. Coburn. Carbon Monoxide-Induced Arterial Hypoxemia. Science, Vol. 164, 1969, pp. 1297-1298.

34. Ehrich, W. E., S. Bellet, and F. H. Lewey. Cardiac Changes from CO Poisoning. Amer. J. Med. Sci., Vol. 208, 1944, pp. 511-523.

35. Astrup, P., K. Kjeldsen,and J. Wanstrup. Enhancing Influence of Carbon Monoxide on the Development of Atheromatosis in Cholesterol-fed Rabbits. J. Atheroscler. Res., Vol. 7, 1967, pp. 343-354.

36. Wilks, S. S., J. F. Tomashefski and R. T. Clark. Physiological Effects of Chronic Exposure to Carbon Monoxide. J. Appl. Physiol., Vol. 14, 1959, pp. 305-310.

37. Killick, E. M. The Nature of the Acclimatization Occurring During Repeated Exposure of the Human Subject to Atmospheres Containing Low Concentrations of Carbon Monoxide. J. Physiol., Vol. 107, 1948, pp. 27-44.

38. Fodor, G. G. and G. Winneke. Differing Affinity Coefficients of CO to Hemoglobin in Man and Animals. Zbl. Bakt., Abt. I., Ref., Vol. 224, 1971, p. 15.

39. Zorn, H. The Oxygen Partial Pressure in Brain Tissue and in the Liver with Subtoxic Carbon Monoxide Concentrations. VDI-Berichte, No. 180, 1972, pp. 67-71.

40. Malorny, G. Effect on Carbon Monoxide on Capability. Staub, Vol. 23, 1963, pp. 156-159.

41. Malorny, G. General Survey of the Effect of Carbon Monoxide on Humans. State of the Research Work in the Working Group "Carbon Monoxide Action". VDI-Berichte, No. 180, 1972, pp. 47-58.

42. Schargus, G. Studien über einen Wühltest beim Goldhamster (Studies on an Agitation Test in the Golden Hamster). Dissertation, Hamburg, 1966.

43. Malorny, G., G. G. Fodor and H. Pomp. Effects of Low CO Concentrations on Spontaneous Motility and Flight Reaction (with Brief Film). Naunyn-Schmiedebergs Arch. exp. Path. Pharm., Vol. 246, 1963, p. 23.

44. Zorn, H. The Learning Ability for Conditioned Reflexes in Wistar Rats under the Intermittent Effect of Low CO Concentrations. VDI-Berichte, No. 180, 1972, pp. 77-79.

45. Sontag, H.-H. Vergleichend-physiologische Untersuchungen uber Aufnahme und Wirkung von Kohlenmonoxid am Ratten- und Meerschweinchen-Organismus (Comparative Physiological Studies on the Intake and Action of Carbon Monoxide in the Rat and Guinea Pig). Dissertation, Hamburg, 1966.

46. Xintaras, C. et al. Application of the Evoked Response Technique in Air Pollution Toxicology. Toxicol. Appl. Pharmacol., Vol. 8, 1966, pp. 77-87.

47. Fodor, G. G. REM Depressions as Early Signs of Intoxication by Industrial Chemical Noxa. Lecture, Industrial Neurology Congress with International Participation, Prague, June 25 - 28, 1969. Congress report in press.

48. Fodor, G. G., G. Winneke, M. Zimmerman and G. Arnold. Animal Experimental Studies on Sleep Disturbances from Atmospheric Chemical Noxa. Congress volume "The Nature of Sleep". Stuttgart, Fischer (in press).

49. Fodor, G. G., H.-W. Schlipköter and M. Zimmermann. The Objective Study of Sleeping Behavior in Animals as Test of Behavioral Toxicity. In: Adverse Effects of Environmental Chemicals and Phychotropic Drugs: Quantitative Interpretation of Functional Tests. Ed. WHO Genf, International Labour Office (in press).

50. Colmant, J. On the Effect of Low Carbon Monoxide Concentrations on the Sleeping-Waking Behavior of the Albino Rat. VDI-Berichte, No. 180, 1972, pp. 74-76.

51. Lewey, F. H. and D. L. Drabkin. Experimental Chronic Carbon Monoxide Poisoning of Dogs. Amer. J. Med. Sci., Vol. 208, 1944, pp. 502-511.

52. Lindenberg, R. et al. An Experimental Investigation in Animals of the Functional and Morphological Changes from Single and Repeated Exposure to Carbon Monoxide. Presented at the American Industrial Hygiene Conference, Washington, D.C., May 13-17, 1962.

53. Astrup, P., D. Trolle, H. M. Olsen and K. Kjeldsen. Unpublished Results (1972). In: P. Astrup: Pathological Effects of Moderate Carbon Monoxide Concentrations. VDI-Berichte, No. 180, 1972, pp. 62-65.

54. Rozera, G. and S. Fati. Erythrocytic Acid and Alkaline Phosphatase in Chronic Intoxication from Carbon Monoxide. Folia Med. (Nap.), Vol. 42, 1959, pp. 1204-1214.

55. Fati, S., R. Mole and L. Pecora. Glycolytic Enzymes of the Red Cell in Intoxication form Carbon Monoxide. III. Behavior of Erythrocytic Phosphoglucomutase in Acute Carbon Monoxide Poisoning. Folia Med. (Nap.), Vol. 43, 1960, pp. 1092-1097.

56. Barrios del Risco, P. Indication of an Effect of Carbon Monoxide on the Central Nervous System, Independent of the Hemoglobin Blockage. VDI-Berichte, No. 180, 1972, pp. 80-82.

57. Rondia, D. Effect of Low Carbon Monoxide Concentrations on Liver Enzymes. VDI-Berichte, No. 180, 1972, pp. 79-80.

58. Bauer, H. Untersuchungen der Blut- und Hirnproteine bei experimenteller Kohlenoxid-Vergiftung (Investigations of Blood and Brain Proteins in Experimental Carbon Monoxide Poisoning). Report on the Expanded Meeting of the Working Group "Carbon Monoxide Action", June 15, 1964, at Godorf/Cologne.

59. Astrup, P., K. Kjeldsen and J. Wanstrup. Effects of Carbon Monoxide on the Arterial Walls. Paper presented at New York Academy of Sciences Conference on Biological Effects of Carbon Monoxide, New York City, January 12-14, 1970.

REFERENCES

(Section 6.2, Nitrogen Oxides)

1. Leithe, W. Die Analyse der Luft und ihrer Verunreinigungen in der freien Atmosphaere und am Arbeitsplatz (The Analysis of the Air and Its Pollutants in the Open Atmosphere and at the Work Site). Stuttgart, Wiss. Verl. Ges., 1968.

2. Lies, K.-H. Zur Analyse von Kohlenwasserstoffen und Stickoxiden in Abgasen von Verbrennungsmotoren sowie Messung und Erforschung belästigender and shädlicher Luftverunreinigungskomponenten in Grossstädten und industriellen Ballungsgebieten im Hinblick auf ihre synergistichen Wirkungen (On Analysis of Hydrocarbons and Nitrogen Oxides in Exhaust Gases from Combustion Engines and on Measurement and Study of Stressing and Harmful Air Pollution Components with Respect to Their Synergistic Effects). Dissertation, Clausthal Technical College, 1970.

3. Brockhaus, A. Nitrogen Oxides. Medical Institute for Air Hygiene and Silicosis Research, Annual Report, 1970. Dusseldorf, Triltsch, 1971, pp. 82-89.

4. Flury, F. and F. Zernik. Schädliche Gase, Dämpfe, Nebel, Rauch- und Staubarten (Harmful Gases, Vapors, Fogs, Smokes, and Dusts). Berlin, J. Springer, 1931.

5. Air Quality Criteria for Nitrogen Oxides. Washington, U..S. Department of Health, Education and Welfare, 1971.

6. Lowry, T. and L. M. Schumann. Silo-Filler's Disease. A Syndrome Caused by Nitrogen Dioxide. J. Amer, Med. Assn., Vol. 162, 1956, pp. 153-160.

7. Vigliana, E. C. and N. Zurlo. Experience of the Clinica del Lavoro with Some Maximum Workplace Concentrations (MAK) of Industrial Poisons. Arch. Gewerbepath., Vol. 13, 1955, pp. 528-534.

8. Wagner, H.-M. Absorption of NO and NO_2 in Inhalation at Maximum Emission Concentrations (MIK) and Maximum Work Place Concentrations (MAK). Staub-Reinhaltung der Luft, Vol. 30, 1970, pp. 380-382.

9. Murphy, S. D., C. E. Uhlrich, S. H. Frankowitz and C. Xintaras. Altered Function in Animals Inhaling Low Concentrations of Ozone and Nitrogen Dioxide. Amer. Ind. Hyg. Assn. J., Vol. 25, 1964, pp. 246-253.

10. Sancier, K. M., G. Freeman and J. S. Mills. Electron Spin Resonance of Nitric Oxide-Hemoglobin Complexes in Solutions. Science, Vol. 137, 1962, pp. 752-754.

11. Patty, F. A. Industrial Hygiene and Toxicology. Vol. II: Toxicology. New York, Interscience Publishers, 1963.

12. Collen, M. F., G. L. Dybdahl and G. F. O'Brien. A Study of Pneumonia in the Shipbuilding Industry. J. Ind. Hyg., Vol. 26, 1944, pp. 1-7.

13. Baetjer, A. M. Chronic Exposure to Air Pollutants and Acute Infectious Respiratory Diseases. Arch. Industr. Hyg., Vol. 2, 1950, pp. 400-406.

14. Vigdortschik, N. A., E. C. Andreeva, I. A. Matussevich, M. M. Nikulina, L. M. Frumina and V. A. Striter. The Symptomatology of Chronic Poisoning with Oxides of Nitrogen. J. Ind. Hyg., Vol. 19, 1937, pp. 469-473.

15. Rokaw, S. N. et al. Human Exposures to Single Pollutants-NO_2 in a Controlled Environment Facility. Paper presented at Ninth AMA Air Pollution Medical Research Conference, Denver, July 24, 1968.

16a. von Nieding, G., H. Krekeler, U. Smidt and K. Muysers. Acute Effect of 5 ppm NO_2 on the Lung and Circulatory Function of the Healthy Human. Int. Arch. Arbeitsmed., Vol. 27, 1970, pp. 234-243.

16b. von Nieding, G., M. Wagner, H. Krekeler, U. Smidt and K. Muysers. Absorption of NO_2 in Low Concentrations in the Respiratory Tract and Its Acute Effects on Lung Function and Circulation. Preprint of paper presented at the Second International Clean Air Congress, Washington D.C., December 6 - 11, 1970.

17. von Nieding, G., M. Wagner, H. Krekeler, U. Smidt and K. Muysers. Limiting Value Determinations for the Acute NO_2 Effect on Respiratory Gas Exchange and the Respiratory Tract Resistance of Humans with Chronic Lung Disease. Int. Arch. Arbeitsmed., Vol. 27, 1971, pp. 338-348.

18. von Nieding, G. and H. Krekeler. Pharmacologic Influence of the Acute NO_2 Effect on the Lung Function of Healthy Persons and Patients with Chronic Bronchitis. Int. Arch. Arbeitsmed, Vol. 29, 1971, pp. 55-63.

19. Abe, M. Effects of Mixed NO_2-SO_2 Gas on Human Pulmonary Functions. Bull. Tokyo Med. dent. Univ., Vol. 14, 1967, pp. 415-435.

20. Thomas, H. V., P. K. Mueller and R. Wright. Response of Rat Lung Mast Cells to Nitrogen Dioxide Inhalation. J. Air Poll. Control Assn., Vol. 17, 1967, pp. 33-35.

21. Shalamberidze, O. P. Reflex Action of a Mixture of Sulfur Dioxide and Nitrogen Dioxide. Gig. i. Sanit., Vol. 32, 1967, pp. 9-13.

22. Henschler, D., A. Stier, H. Beck and W. Neumann. Odor Thresholds of Some Important Irritant Gases (Sulfur Dioxide, Ozone, Nitrogen Dioxide) and Phenomena on the Action of Low Concentrations on Humans. Arch. Bewerbepath. Gewerbehyg., Vol. 17, 1960, pp. 547-570.

23. Rumsey, D. W. and R. P. Cesta. Odor Threshold Levels for UDMH and NO_2. Amer. Ind. Hyg. Assn. J., Vol. 31, 1970, pp. 339-343.

24. Finney, D. J. Probit Analysis. Cambridge, Cambridge University Press, 1952.

25. Fodor, G. G. and G. Winneke. Stresses from Materials with Strong Odors. Zbl. Bakt. Hyg., I. Abt. Orig. B, Vol. 155, 1971, pp. 282-295.

26a. Shy,C. M., J. P. Creason, M. E. Pearlman, K. E. McClain, F. B. Benson and M. M. Young. The Chattanooga School Children Study: Effects of Community Exposure to Nitrogen Dioxide. 1. Methods, Description of Pollutant Exposure, and Results of Ventilatory Function Testing. J. Air Poll. Control Assn., Vol. 20, 1970, pp. 539-545.

26b. Shy, C. M., J. P. Creason, M. E. Pearlman, K. E. McClain, F. B. Benson and M. M. Young. The Chattanooga School Children Study: Effects of Community Exposure to Nitrogen Dioxide. II. Incidence of Acute Respiratory Illness. J. Air Poll. Control Assn., Vol 20, 1970, pp. 582-588.

27. Pearlman, M. E., J. F. **Finklea**, J. P. Clearson, C. M. Shy, M. M. Young and R. J. M. Horton. Nitrogen Dioxide and Lower Respiratory Illness. Pediatrics, Vol. 47, 1971, pp. 391-398.

28. Jacobs, M. B. and S. Hochheisser. Continuous Sampling and Ultramicro-Determination of Nitrogen Dioxide in Air. Anal. Chem., Vol. 30, 1958, pp. 426-428.

29. Gray, E. Le B., F. M. Patton, S. B. Goldberg and E. Kaplan. Toxicity of the Oxides of Nitrogen. II. Acute Inhalation Toxicity of Nitrogen Dioxide, Red Fuming Nitric Acid, and White Fuming Nitric Acid. A.M.A. Arch. Ind. Hyg. Occup. Med., Vol. 10, 1954, pp. 418-422.

30. Ross W. and D. Henschler. Effect of Long-Term Inspiration of Low Concentrations of Nitrogen Dioxide on the Mouse Lung. Naturwissenshaften, Vol. 50, 1963, pp. 503-504.

31. Henschler, D. Protective Effect of Pretreatment with Low Gas Concentrations Against Fatal Lung Edema from Irritant Gases. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak., Vol. 238, 1960, pp. 66-67.

32. Stokinger, H. E. New Concepts and Future Trends in Toxicology. Amer. Industr. Hyg. Assn. J., Vol. 23, 1962, pp. 8-19.

33a. Henschler, D., E. Hahn and W. Assmann. Effective Conditions for a Rise in Tolerance on Repeated Breathing of Irritant Gases Producing Pulmonary Edema. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak., Vol. 249, 1964, pp. 249-342.

33b. Henschler, D., E. Hahn, H. Heymann and H. Wunder. Mechanism of a Rise in Tolerance on Repeated Breathing of Gases Producing Pulmonary Edema. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak., Vol. 249, 1964 pp. 343-356.

34. Dillman, G., D. Henschler and W. Thoenes. Effects of Nitrogen Dioxide on the Lung Alveoli of the Mouse. Arch. Toxikol., Vol. 23, 1967, pp. 55-65.

35. Buell, G. C., Y. Tokiwa and P. K. Mueller. Lung Collagen and Elastin Denaturation in Vivo Following Inhalation of Nitrogen Dioxide. Paper No. 66-7 presented at the 59th Annual Air Pollution Control Association Meeting, San Francisco, June, 1966. Quoted in: Mueller, P. K. and M. Hitchcock. Air Quality Criteria — Toxicological Appraisal for Oxidants, Nitrogen Oxides and Hydrocarbons. J. Air Poll. Control Assn., Vol. 19, 1969, pp. 670-676.

36. Henry, M. C., R. Ehrlich and W. H. Blair. Effect of Nitrogen Dioxide on Resistance of Squirrel Monkeys to Klebsiella Pneumoniae Infection. Arch. Environ. Health, Vol. 18, 1969, pp. 580-587.

37. Henschler, D. and W. Ross. On the Question of a Carcinogenic Effect of Inhaled Nitrogen Oxide. Naunyn-Schmiedebergs Arch. exp. Path. Pharmak., Vol. 253, 1966, pp. 495-507

39. Blair, W. H., M. C. Henry and R. Ehrlich. Chronic Toxicity of Nitrogen Dioxide. Arch. Environ. Health, Vol. 18, 1969, pp. 186-192.

40. Freeman, G. and G. B. Haydon. Emphysema after Low-Level Exposure to NO_2. Arch. Environ. Health, Vol. 8, 1964, pp. 125-128.

41. Haydon, G. B., G. Freeman and N. J. Furiosi. Covert Pathogenesis of NO_2-Induced Emphysema in Rat. Arch. Environ. Health, Vol. 11, 1965, pp. 776-783.

42. Freeman, G. and N. J. Furiosi. Effects of Continuous Exposure of 0.8 ppm NO_2 on Respiration of Rats. Arch. Environ-Health, Vol. 13, 1966, pp. 454-456.

43. Gray, E. L., Mac Namee, J. K. and S. B. Goldberg. Toxicity of NO_2 Vapors at Very Low Levels. Arch. Industr. Hyg., Vol. 6, 1952, pp. 20-21.

44. Wagner, W. D., B. R. Duncan, P. G. Wright and H. E. Stokinger. Experimental Study of Threshold Limits of NO_2. Arch. Environ. Health, Vol. 10, 1965, pp. 455-466.

45. Purvis, M. R. and R. Ehrlich. Effects of Atmospheric Pollutants and Susceptibility to Respiratory Infection: II. Effect of Nitrogen Dioxide. J. Infect. Dis., Vol. 113, 1963, pp. 72-76.

46. Ehrlich, R. Effect of Air Pollutants on Respiratory Infection. Arch. Environ. Health, Vol. 6, 1963, pp. 638-642.

47. Ehrlich, R. Effect of Nitrogen Dioxide on Resistance to Respiratory Infection. Bact. Rev., Vol. 30, 1966, pp. 604-614.

48. Ehrlich, R. and M. C. Henry. Chronic Toxicity of Nitrogen Dioxide. I. Effect to Resistance to Bacterial Pneumonia. Arch. Environ. Health, Vol. 17, 1968, pp. 860-865.

49. Henry, M. C., J. Findlay, J. Spangler, and R. Ehrlich. Chronic Toxicity of NO_2 in Squirrel Monkeys. III. Effect on Resistance to Bacterial and Viral Infection. Arch. Environ. Health, Vol. 20, 1970, pp. 566-570.

50. Weissbäcker, L., R. D. Carpenter, P. C. Luchsinger, and T. S. Osdene. In Vitro Alveolar Macrophages Viability. Arch. Environ. Health, Vol. 18, 1969, pp. 756-759.

51. Valand, S. B., J. D. Acron and Q. N. Myrvik. Nitrogen Dioxide Inhibition of Viral-Induced Resistance in Alveolar Monocytes. Arch. Environ. Health, Vol. 20, 1970, pp. 303-309.

52. Druckey, H. and R. Preussmann. On the Origin of Carcinogenic Nitrosamines with Tobacco Smoke as an Example. Naturwissenschaften, Vol. 49, 1962, pp. 498-499.

53. Wands, R. C. Discussion. J. Air Poll. Control Assn., Vol. 19, 1969, pp. 677-678.

REFERENCES

(Section 6.3, Lead)

1. Aub, J. C., L. T. Fairhall, A. S. Minot and P. Reznikoff. Lead Poisoning. With a chapter on the prevalence of industrial lead poisoning in the United States by A. Hamilton. Baltimore, Williams and Wilkins, 1926.

   — Medicine Monographs, Vol. VII.

2. Barltrop, D. and A. Smith. Lead Binding to Human Haemoglobin. Experientia, Vol. 28, 1972, pp. 76-77.

3. Barry, P. S. I. and D. B. Mossman. Lead Concentrations in Human Tissues. Brit. J. ind. Med., Vol. 27, 1970, pp. 339-351.

4. Bazell, R. J. Lead Poisoning: Zoo Animals May be the First Victims. Science, Vol. 173, 1971, pp. 130-131.

5. Beck, E. G. Die Reaktion in vitro gezuchteter Zellen auf partikelformige Luftverunreinigungen und hochpolymere Stoffe. (The Reaction of Cells Cultured in Vitro to Particulate Air Pollutants and High Polymers). Opladen, Cologne, Westdt. Verl., 1970.

   — Research Report from the State of North Rhine-Westfalia, No. 2083.

6. Report of the Federal Commission on Lead in Gasoline to the Federal Council on Its Activity in the Period 1947 - 1960. Mitt. Lebensmittelunters. u. Hyg., Vol. 52, 1961, pp. 135-244.

7. Booker, D. V. et al. Uptake of Radioactive Lead Following Inhalation and Injection. Brit. J. Radiol., Vol. 42, 1969, pp. 457-466.

8. Bovay, E. Deposits of Lead on the Vegetation Along Automobile Routes. Mitt. Lebensmittelunters. Hyg., Vol. 61, 1970, pp. 303-321.

9. Bruin, A. de. Certain Biological Effects of Lead upon the Animal Organism. Arch. Environ. Health, Vol. 23, 1971, pp. 249-264.

10. Brunner, M. The Composition of the Exhaust Gas of Gasoline Engines. Zschr. Praeventivmed., Vol. 11, 1966, pp. 77-103.

11. Chow, T. J. Lead Accumulation in Roadside Soil and Grass. Nature, Vol. 225, 1970, pp. 295-296.

12. Chow, T. J. and J. L. Earl. Lead Aerosols in the Atmosphere: Increasing Concentrations. Science, Vol. 169, 1970, pp. 577-580.

13. Chow, T. J., J. L. Earl and C. F. Bennett. Lead Aerosols in Marine Atmosphere. Environ. Sci. Technol. Vol. 3, 1969, pp. 737-740.

14. Colucci, J. M., C. R. Begeman and K. Kumler. Lead Concentration in Detroit, New York, and Los Angeles Air. J. Air Poll. Control Assn., Vol. 19, 1969, pp. 255-260.

15. Dabelstein, W. On the Problem of Lead in Gasoline. Erdöl u. Kohle, Vol. 24, 1971, pp. 37-40.

16. Daines, R. H., H. Motto, and D. M. Chilko. Atmospheric Lead: Its Relationship to Traffic Volume and Proximity to Highways. Environ. Sci. Technol., Vol. 4, 1970, pp. 318-323.

17. Deposition and Retention Models for Internal Dosimetry of the Human Respiratory Tract. Task Group on Lung Dynamics. Health Physics, Vol. 12, 1966, pp. 173-207.

18. Eichler, J. Inaktivitätsosteoporose (Inactivity Osteoporosis). Stuttgart, Thieme, 1970, p. 5.

— Aktuelle Orthopädie

19. Engel, R. E., D. I. Hammer, R. J. M. Horton, N. M. Lane and L. A. Plumlee. Environmental Lead and Public Health. Washington, Superintendent of Documents, U. S. Government Printing Office, 1971.V., 34 p.

— Air Pollution Control Office Publication, NO. AP-90.

20. Ferm, V. H. and D. W. Ferm. The Specificity of the Teratogenic Effect of Lead in the Golden Hamster. Life Sciences, Vol. 10, 1971, pp. 35-39.

21. Fuchs, M. S. Delayed Accidents from Saturnism (in Relation to Two Observations). Soc. Med. Hyg. Trav., Paris, 1953, p. 302.

22. Goldwater, L. J. and A. W. Hoover. An International Study of "Normal" Levels of Lead in Blood and Urine. Arch. Environ. Health, Vol. 15, 1967, pp. 60-63.

23. Haas, Th. et al. Delta-aminolevulinic acid Dehydratase as a Valuable Biochemical Parameter in Monitoring of Lead Workers. Arbeitsmed., Vol. 6, 1971, pp. 303-305.

24. Haas, Th. et al. The Usual Lead Load in Newbornsand Their Mothers. Zbl. Bakt. Hyg., I. Abt. Orig. B, Vol. 155, 1972, pp. 341-349.

25. Habibi, K. Characterization of Particulate Lead in Vehicle Exhaust-Experimental Techniques. Environ. Sci. Technol., Vol. 4, 1970, pp. 239-248.

26. Haeger-Aronsen, B., M. Abdulla and B. J. Fristedt. Effect of Lead on d-aminolevulinic Acid Dehydrase Activity in Red Blood Cells. Arch. Environ. Health, Vol. 23, 1971, pp. 440-445.

27. Haley, Th. J. Chronic Lead Poisoning Through Contamination of the Environment with Lead — Myth or Fact? In: Blei und Gesundheit (Lead and Health). Biebesheim/Rh., Ak Chemie, 1971, pp. 4-9.

28. Hemphill, F. E., M. L. Kaeberle and W. B. Buck. Lead Suppression of Mouse Resistance to Salmonella typiimorium. Science, Vol. 172, 1971, p. 1031.

29. Hernberg, S. and J. Kikkanen. Enzyme Inhibition by Lead Under Normal Urban Conditions. Lancet, Vol. 1, 1970, pp. 63-64, 704-705.

30. Hirschler, D. A. and L. F. Gilbert. Nature of Lead in Automobile Exhaust Gas. Arch. Environ. Health, Vol. 8, 1964, pp. 297-313.

31. Horiuchi, K, H. Noma, I. Asano and K. Hashimoto. Studies on The Industrial Lead Poisoning. Osaka City Med. J., Vol. 8, 1962, pp. 151-168.

32. Horiuchi, K. Sixteen Years' Experiences in the Research on Industrial Lead Poisonings. Osaka City Med. J., Vol. 11, 1965, p. 225.

33. Horiuchi, K. Lead in the Environment and Its Effect on Man in Japan. Osaka City Med. J., Vol. 16, 1970, pp. 1-28.

34. Hursh, J. B. and T. T. Mercer. Measurement of ^{212}Pb Loss Rate from Human Lungs. J. Appl. Psychol., Vol. 28, 1970 pp. 268-274.

35. Hursh, J. B. and J. Suomela. Absorption of ^{212}Pb from the Gastrointestinal Tract of Man. Acta Radiol., Stockholm, Vol. 7, 1968, pp. 108-120.

36. Högger, D. The Problem of Lead in Gasoline. In: The Problem of Lead in Gasoline. Studies of the Federal Commission for Air Hygiene, Suppl. B, No. 3, 1971, pp. 3-19.

37. Imamura, V. Studies on the Industrial Lead Poisoning. I. Absorption, Transportation, Deposition and Excretion of Lead. 3. An Experimental Study of Lead Intake in Human Beings. Osaka City Med. J., Vol. 3, 1957, p. 167.

38. Jost, D. The Concentration of Aerosol-Bound Lead in the City Region of Frankfurt am Main. In: Blei and Umwelt. (Lead and Environment). Published by the Commission for Hazards of the Federal Health Office, Working Group on Lead. Berlin, Verein f. Wasser-, Boden- und Lufthygiene e.V., 1972, pp. 9-11.

39. Jutzi, W. Lead Content of Road Dust and Road Air in the City of Zurich in the Spring of 1970. In: Das Problem der Benzinverbleiung. Untersuchungen der Eidgennoessischen Kommission für Lufthygiene (The Problem of Lead in Gasoline. Studies of the Federal Commission for Air Hygiene). Bulletin of the Federal Hygiene Service, Suppl. B, 1971, No. 3, pp. 77-83.

40. Kehoe, R. A. The Metabolism of Lead in Man in Health and Disease. J. Roy. Inst. Publ. Health, Vol. 24, 1961, pp. 81-96.

41. Kehoe, R. A. The Metabolism of Lead in Man in Health and Disease. Arch. Environ. Health, Vol. 2, 1961, pp. 418-422.

42. Kehoe, R. A. Metabolism of Lead Under Abnormal Conditions. Arch. Environ. Health, Vol. 8, 1964, pp. 235-243.

43. Kehoe, R. A. Normal Metabolism of Lead. Arch. Environ. Health, Vol. 8, 1964, pp. 232-235.

44. Keller, Th. The Present Lead Content of the Vegetation in the Vicinity of Swiss Automobile Roads. Zschr. Praeventivmed., Vol. 15, 1970, pp. 235-243.

45. Keller, Th. On Traffic-Caused Lead Residues on Forest Vegetation. In: Das Problem der Benzinverbleiung. Untersuchungen der Eidgenössischen Kommission für Lufthygiene, (The Problem of Lead in Gasoline. Studies of the Federal Commission for Air Hygiene), pp. 118-130.

46. Kempf, Th. Lead Content in Water. In: Blei und Umwelt (Lead and Environment). Published by the Commission for Environmental Hazards of the Federal Health Office, Working Group on Lead. Berlin, Verein f. Wasser-, Boden- u. Lufthygiene e. V., 1972, pp. 31-32.

47. Kloke, A., K. Riebartsch and H. O. Leh. Contamination of Crop Plants by Automobile Exhaust Gases. Landwirtschaftl. Forsch., Sonderh., Vol. 20, 1966, p. 119.

48. Kobayashi, Y., M. Hori, and K. Tsuchiya. Distribution of Lead in the Air Near City Roads. Keio J. Med., Vol. 19, 1970, pp. 183-194.

49. Kostial, K., I Simonovic and M. Pisonic. Lead Absorption from the Intestine in Newborn Rats. Nature, Vol. 233, 1971, p. 564.

50. Lahmann, E. and M. Moeller. Air Pollution in Cities from Lead-Containing Dusts. Bundesgesundheitsbl., Vol. 10, 1967, pp. 261-264.

51. Laveskog, A. A Method for Determination of Tetramethyl Lead (TML) and Tetraethyl lead (TEL) in Air. In: Second International Clean Air Congress, pp. 549-556.

52. Lawther, P. J., B. T. Commins, J. Mck. Ellison and B. Biles. Airborne Lead and its Uptake by Inhalation. Conference: "Lead in the Environment", Zoological Society of London, January 27, 1972, special edition, 20 pp.

53. Lee, R. E. et al. Concentration and Particle Size Distribution of Particulate Emissions in Automobile Exhaust. Atmosph. Environ., Vol. 5, 1971, pp. 225-237.

54. Leh, H.-D. Contamination of Plants with Lead from Automobile Exhaust Gases. In: Blei und Umwelt (Lead and Environment). Published by the Commission for Environmental Hazards of the Federal Health Office, Working Group on Lead. Berlin, Verein f. Wasser-, Boden- und Lufthygiene e. V., 1972, pp. 38-48.

55. Lehnert, G. et al. Occupational Lead Stress from Automobile Exhaust Gases in Large City Streets. Dtsch. Med. Wschr., Vol. 95, 1970, pp. 1097-1099.

56. Lehnert, G. et al. Usual Lead Load from Food and Drink. Arch. Hgy., Vol. 153, 1969, pp. 403-412.

57. Lehnert, G., K.-H. Schaller and D. Szadkowski. Diagnosis and Therapy of Industrial Lead Poisoning. Med. Mschr., Vol. 24, 1970, pp. 51-54.

58. Lob, M. and P. Desbaumes. Study on Plumbism and Plumburia in Two Groups of Prisoners, One Confined in the Country and the Other in the Immediate Neighborhood of an Automobile Route. In: Das Problem der Benzinverbeliung. Untersuchung der Eidgenössischen Kommission für Lufthygiene (The Problem of Lead in Gasoline. Studies of the Federal Commission for Air Hygiene). Bulletin of the Federal Hygiene Service, Supplement B, No. 3, 1971, pp. 84-85.

59. Ludwig, J. H., D. R. Diggs, H. E. Hesselberg and J. A. Maga. Survey of Lead in the Atmosphere of Three Urban Communities: A Summary. Am. Ind. Hyg. Assn. J., Vol. 26, 1965, pp. 270-284

60. Lutmer, R. F., K. A. Busch and R. G. Miller. Lead from Auto-Exhaust: Effect on Mouse Bone Lead Concentration. Atmosph. Environ., Vol. 1, 1967, pp. 585-589.

61. Mappes, R. Oral Report at the Society of German Engineers Meeting of the Working Group "Effect of Lead and Lead Compounds on Humans", April 19, 1971, Dusseldorf.

62. Mappes, R. Studies on the Maximum Allowable Working Place Concentration for Lead. Zbl. Arbeitsmed., Vol. 20, 1970, pp. 379-382.

63. Mattess, G. Lead Content in Rock, Soil and Ground Water. In: Blei und Umwelt (Lead and Environment). Published by the Commission for Environmental Hazards of the Federal Health Office, Working Group on Lead. Berlin, Verein f. Wasser-, Boden- u. Lufthygiene e. V., 1972, pp. 21-27.

64. Menyasz, E. et al. Clinical Considerations and Laboratory Studies on the Effect of Lead on Pregnancy. Zbl. Gynaek., 1965, pp. 27-34.

65. Mehani, S. Lead Retention by the Lungs of Lead-Exposed Workers. Ann. Occup. Hyg., Vol. 9, 1966, pp. 165-171.

66. Milev, N., E.-L. Sattler and E. Menden. Uptake and Storage of Lead in the Body in Various Nutritional Conditions. Med. u. Ernaehr., Vol. 11, 1970, pp. 29-32.

67. Moeschlin, S. Klinik und Therapie der Vergiftungen (Clinical Treatment and Therapy of Poisonings). Fourth Edition. Stuttgart, Thieme, 1965, XIX, 750 pp.

68. Nozaki, K. Method for Studies on Inhaled Particles in Human Respiratory System and Retention of Lead Fumes. Ind. Health, Vol. 4, 1966, pp. 118-128.

69. Page, A. L., T. J. Ganje and M. S. Joshi. Lead Quantities in Plants, Soil, and Air Near Some Major Highways in Southern California. Hilgardia, Vol. 41, 1971, pp. 1-31.

70. Pott, F. and A. Brockhaus. Comparison of the Enteric and Pulmonary Absorption Ratios and Lead Compounds. Zbl. Bakt. Abt. I, Orig., Rehie B, Vol. 155, 1971, pp. 1-17.

71. Prerovsak, I. and J. Teisinger. Excretion of Lead and Its Biological Activity Several Years After Termination of Exposure. Brit. J. Ind. Med., Vol. 27, 1970, pp. 352-355.

72. Reichel, G., F. Wobith and W. T. Ulmer. Acute and Chronic Effect of Street Air at a High-Traffic Crossing on the Human Lung Function and on the CO, Hb and Lead Content of the Blood. Int. Arch. Arbeitsmed., Vol. 26, 1970, pp. 84-97.

73. Richter, R. H. H. and Ch. Schlatter. On the Question of the Effect of Lead from Automobile Exhaust Gases on Domestic Animals. In: Das Problem der Benzinverbleiung. Untersuchung der Eidgenössischen Kommission für Lufthygiene (The Problem of Lead in Gasoline. Study of the Federal Commission for Air Hygiene). Bulletin of the Federal Hygiene Service, Supplement B, No. 3, 1971, pp. 86-100.

74. Tobinson, E. and F. L. Ludwig. Particle Size Distribution of Urban Lead Aerosols. J. Air Poll. Contr. Assn., Vol. 17, 1967, pp. 664-669.

75. Sattler, E. L. Lead Intake and Distribution. In: Blei und Umwelt (Lead and Environment). Published by the Commission for Environmental Hazards of the Federal Health Office, Working Group on Lead. Berlin, Verein f. Wasser-, Boden-, u. Lufthygiene E. V., 1972, pp. 79-81.

76. Sawinsky, A., J. Durszt and G. Pasztor. Leucocyte Injury on Lead Exposure. Zschr. Hyg. u. Grenzgeb., Vol. 4, 1971, pp. 239-240.

77. Scanlong, J. Umbilical Cord Blood Lead Concentration. Amer. J. Dis. Child., Vol. 121, 1971, pp. 325-326.

78. Schmidt, W. Attempt to Calculate the Alveolar Surface of the Human Lung. Z. Anat. Entw. gesch., Vol. 125, 1966, pp. 119-131.

79. Schroeder, H. A. and I. H. Tipton. The Human Body Burden of Lead. Arch. Environ. Health, Vol. 17, 1968, pp. 965-978.

80. Schubert, R. H. W. and H. Sangl. On the Question of the Lead Stress from Automobile Exhaust Gas. A Contribution to the Applicability of the Delta-Aminolevulinic Acid Determination in Urine as a Criterion for the Environmental Lead Load. Zbl. Bak. Hyg., I. Abt. Orig. B, Vol. 155, 1972, pp. 470-475.

81. Schwanitz, G., G. Lehnert and E. Beghart. Chromosome Damage From Occupational Lead Loading. Dtsch. Med. Wschr., Vol. 95, 1970, pp. 1636-1641.

82. Schlipköter, H.-W., J. Bruch, A. Prockhaus and G. G. Fodor. The Lungs as Intake Organs for Solid, Liquid and Gaseous Imissions. Praxis Pneumol., Vol. 25, 1971, pp. 505-518.

83. Smith, R. G., J. Szajnar and L. Hecker. Study of Lead Levels in Experimental Animals. Environ. Sci. Technol., Vol. 4, 1970, pp. 333-340.

84. Tansy, M. F. and R. P. Roth. Pigeons: A New Role in Air Pollution. J. Air Poll. Control Assn., Vol. 20, 1970, pp. 307-309.

85. Taschenbuch der praktishen Medizin (Pocket Book of Practical Medicine). Edited by G. Schettler. Therein: Buckup, H. Occupational Diseases. Stuttgart, G. Thieme, Seventh Revised Edition, 1972, pp. 90-93.

86. TerHaar, G. Air as a Source of Lead in Edible Crops. Environ. Sci. Technol., Vol. 4, 1970, pp. 226-229.

87. TerHaar, G., D. L. Lenane J. N. Hu and M. Brnadt. Composition, Size and Control of Automotive Exhaust Particulates. J. Air Poll. Control Assn., Vol. 22, 1972, pp. 39-46.

88. Thomas, H. V. et al. Blood Lead of Persons Living Near Freeways. Arch. Environ. Health, Vol. 15, 1967, pp. 695-702.

89. Thompson J. A. Balance Between Intake and Output of Lead in Normal Individuals. Brit. J. Ind. Med., Vol. 28, 1971, pp. 189-194.

90. Tsuchiya, K. and S. Harashima. Lead Exposure and the Derivation of Maximum Allowable Concentrations and Threshold Limit Values. Brit. J. Ind. Med., Vol. 22, 1965, pp. 181-186.

91. Walkenhorst, W. Fundamentals of the Deposition of Small Particles in the Bronchial and Alveolar Space. Med. Klin., Vol. 66, 1971, pp. 303-307.

92. Weber, J. Lead in Tobacco Smoke. In: Blei und Umwelt (Lead and Environment). Published by the Commission for Environmental Hazards of the Federal Health Office, Working Group on Lead. Berlin, Verein f. Wasser-, Boden- u. Lufthygiene e. V., 1972, pp. 62-63.

REFERENCES

(Section 6.4, "Oxidants")

1. Selected Methods for the Measurement of Air Pollutants. Public Health Service Publication No. 999-AP-11. Cincinnati, May, 1965.

2. Air Quality Criteria for Photochemical Oxidants. National Air Poll. Contr. Admin. Publ. No. AP-63. Washington, D.C., March, 1970.

3. Wayne, L. G. The Chemistry of Urban Atmospheres. Technical Progress Report III. Los Angeles Air Pollution Control District, December, 1962.

4. Richardson, N. A. and W. C. Middleton. Evaluation of Filters for Removing Irritants from Polluted Air. University of California, Engineering Dept., Los Angeles, Calif, Report No. 57-43, June, 1957.

5. Richardson, N. A. and W. C. Middleton. Evaluation of Filters for Removing Irritants from Polluted Air. Heating, Piping Air Conditioning, Vol. 30, 1958, pp. 147-154.

6. Schuck, E. A., G. J. Doyle and N. Endow. Progress Report on Photochemistry of Polluted Atmospheres. Stanford Research Institute, December, 1960.

7. Korth, M. W., R. C. Stahman and A. H. Rose. Effects of Hydrocarbons to Oxides of Nitrogen Ratios on Irradiated Auto Exhaust. Part 1. J. Air Poll. Contr. Assoc., Vol. 14, 1964, pp. 168-175.

8. Schoettlin, C. E. and E. Landau. Air Pollution and Asthmatic Attacks in the Los Angeles Area. Public Health Reports. 76, 1961, pp. 545-548.

9. Wayne, W. S., P. F. Wehrle and R. E. Carroll. Oxidant Air Pollution and Athletic Performance. J. Amer. Med. Assoc., Vol. 199, No. 12, 1967.

10. Young, W. A., D. B. Shaw and D. V. Bates. Effect of Low Concentrations of Ozone on Pulmonary Function in Man. J. Appl. Physiol., Vol. 19, 1964, pp. 765-768.

11. Goldsmith, J. R. and J. Nadel. California State Dept. of Public Health. Berkeley, 1967.

12. Coffin, D. L. et al. Effect of Air Pollution on Alteration of Susceptibility to Pulmonary Infection. Lecture, Third Annual Conference on Atmospheric Contamination in Confined Spaces, Dayton, May, 1967.

13. Coffin, D. L. and E. J. Blommer. Acute Toxicity of Irradiated Auto Exhaust. Its Indication by Enhancement of Mortality from Streptococcal Pneumoniae. Arch. Environm. Health., Vol. 15, 1967, pp. 36-38.

14. Stokinger, H. E. Ozone Toxicology. A Review of Research and Industrial Experience: 1954 - 1964. Arch. Environm. Health, Vol. 10, 1965, pp. 719-731.

15. Buell, G. C, Y. Tokiwa and P. K. Mueller: Potential Cross-linking Agents in Lung Tissue: Formation and Isolation after in Vivo Exposure to Ozone. Arch. Environm. Health, Vol. 19, 1969, pp. 213-219.

16. Hueter, F. G, G. L. Contner, K. A. Busch and R. Hinners. Biological Effects of Atmospheres Contaminated by Auto Exhaust. Arch. Environm. Health., Vol. 12, 1966, pp. 553-560.

17. Lewis, T. R., F. G. Heuter and K. A. Busch. Irradiated Automobile Exhaust. Its Effects on the Reproduction of Mice. Arch. Environm. Health, Vol. 15, 1967, pp. 26-35.

18. Broblicki, P. J. and G. J. Nebel. The Photochemical Formation of Aerosols in Urban Atmospheres. Symposium, "Chemical Reaction in Urban Atmospheres", Warren, Michigan, October 6 - 7, 1969.

19. Goetz, A. and P. Pueschel. Photochemical Aerosol Formation as Nucleation Phenomenon. Lecture, 145th National Meeting, American Chemical Society, New York City, N. Y., September 8 - 13, 1963.

20. Stevenson, H. J. R. Dissertation. Kettering Laboratory, University of Cincinnati, 1964.

21. Schuck, E. A. and G. J. Doyle. Photooxidation of Hydrocarbons in Mixtures Containing Oxides of Nitrogen and Sulfur Dioxide. Report No. 29., Air Poll. Foundation, San Marino, Calif., October, 1959.

22. Reckner, L., W. E. Scott and R. H. Linell. Aerosol Formation from SO_2 in Photochemical Systems. Lecture, Air Pollution Symposium, 145th National Meeting, American Chemical Society, New York City, N. Y., September 8 - 13, 1963.

23. Schuck, E. A., H. W. Ford and E. R. Stephens. Report No. 26. Air Poll. Foundation, San Marino, Calif, October, 1958.

24. Renzetti, N. A. and G. J. Doyle. Int. J. Air Poll., Vol. 2, 1961, p. 327.

25. Heck, W. W., F. L. Fox, C. S. Brandt and J. A. Dunning. Tobacco, a Sensitive Monitor for Photochemical Air Pollution. National Air Poll. Contr. Admin. Publ. No. AP-55, Cincinnati, Ohio, June, 1969.

26. Wagner, H. M. Experimental Arrangement for the Production of "Synthetic Smog". Schr. Reihe Verein Wasser-Boden-Lufthygiene, Vol. 33, 1970, pp. 149-152.

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7. Appendix: Hydrocarbons

7.1. Introductory Remarks

Until just a few years ago, the effect of hydrocarbons was purely a problem of occupational medicine, but its significance as a general aspect of clean air problems is rising day by day, due to a constant increase of emission into the atmosphere. Apart from areas under the aegis of occupational medicine, the highest hydrocarbon concentrations are found today in the street, especially in high traffic areas [Wagner, 1]. The escape of hydrocarbons in significant quantities from various emission sources constitutes an important air-polluting group of materials. The immediate sources are refineries, petrochemical facilities, and the paint and dye industry. In secondary emissions, it is the automobile which plays the essential role (incomplete combustion of hydrocarbons in energy production), apart from domestic and industrial heating plants [Oelert, 2].

In 1968, organic compounds emitted in the U.S.A. amounted to 32 million tons. Vehicles contributed 52%, industrial processes — 41%. The remaining 7% came from trash disposal and stationary combustion sources [Wagner, 1]. According to reports from the federal government [3], the total emission of hydrocarbons in West Germany during 1969/1970 amounted to 2 million tons; an increase of 75 % 935,000,000 tons per year) is anticipated. According to Oelert [2], traffic contributes approximately 50% of the total emission. On the basis of present and projected figures [3], we can count on 550,000 tons of hydrocarbon emission from vehicles alone in 1972:

cars and vans, ca. 85%;
trucks, ca. 12%; and
buses, ca. 3%.

The government of North Rhine-Westphalia estimates that the internal combustion engine produces approximately 24 kg of hydrocarbons per

1000 liters fuel, the Diesel engine — approximately 16 kg. We must also remember that especially in heavy traffic areas, most vehicles are likely to be Diesel driven (trucks and buses); Diesel motor exhaust gases are, therefore, by no means as insignificant as they are often represented.

Even today, hydrocarbon immission concentrations range from 1 - 10 ppm, and can reach 30 ppm [1]. These numbers represent the sum of all hydrocarbons in the atmosphere, and give no indication of their individual importance. The collective term "hydrocarbon" encompasses a huge number of saturated and unsaturated, aliphatic, cyclic and aromatic compounds with an extraordinary range of attributes.

For any assessment of toxic effects, or of thresholds, it is, however, necessary to at least recognize the relevant individual components and their concentrations. It is impossible to evaluate the effectiveness of the total hydrocarbons as long as there are no measurement standards or reliable figures for the toxicologically relevant fuel components; it is meaningless to propose thresholds for this immission mixture. Assessing the effects will only be possible when we have reliable percentage breakdowns and can be certain that this immission composition persists more or less as such over extended periods of time.

The issue of whether these conditions exist was submitted to the Technical University Clausthal.

The questions were: a) are there techniques for differentiating hydrocarbon emissions in field tests? b) if not, can emission or immission pollution due to uncombusted hydrocarbons be calculated from the composition of fuels used in internal combustion engines? The answers to these questions were to emphasize the toxicologically relevant components (aromatics), taking by-products into account as far as possible.

Herewith, a summary of the most important responses to our questions [Oelert, 2].:

1. Presently available methods for direct determinations of individual hydrocarbons are unsuitable for measurements in the field.

2. It is inappropriate to limit emission effects of internal combustion engine vehicles to the noncombusted gasoline components expelled in the exhaust. The hydrocarbons emitted are more appropriately represented by the gasoline hydrocarbon fractions resulting from incomplete combustion.

3. Relationships (based on experimental models) between aromatics in gasoline and the proportions of aromatics, olefins, aldehydes and phenols in the total emission of organic compounds remain dubious, since not enough consideration can be given to the actual impact of engine and driving conditions.

4. Certain relationships merely reflect the ratios of groups of compounds in fuels vs. exhaust, but give no information on the quantities actually emitted, i.e., relevant in immission.

5. Even if the extensive investigations now in progress were to yield useful approximation formulas, these would still refer to collective values for whole groups of compounds. Meaningful toxicological assessments, however, demand values for individual compounds in these groups. At present, this objective is not within reach.

6. One basis for such calculations would be a constant composition of fuels. Particularly with regard to the toxicologically relevant materials (aromatics), however, this is by no means the case, as Tables 1 and 2 will show.

TABLE 1. INVESTIGATION RESULTS ON AROMATICS IN A REPRESENTATIVE SAMPLE OF REGULAR GASOLINES SHIPPED TO WEST GERMAN GAS STATIONS 1971/72 [Oelert, 2]

No.	Weight, %						
	Total aromatics	Benzene	Toluene	Ethylbenzene	P-xylene	m-xylene	O-xylene
1	23,4	2,2	4,5	1,0	0,9	2,7	1,4
2	23,7	3,2	7,8	1,2	1,3	3,3	1,5
3	25,4	3,2	9,1	1,3	1,6	3,9	1,9
4	27,3	2,9	7,5	1,3	(6,0)		2,4
5	28,4	3,0	9,3	1,5	1,8	4,3	2,2
6	31,3	4,0	9,2	1,7	(7,5)		2,3
7	32,1	4,4	19,9	1,0	0,6	1,7	0,7
8	32,3	4,6	21,1	0,9	0,7	1,9	0,8
9	34,2	3,7	10,5	1,8	(7,7)		2,8
10	34,7	1,6	7,3	2,2	1,6	4,9	1,7
11	34,7	2,0	10,1	2,0	2,1	5,4	2,6
12	35,0	0,5	4,1	3,0	1,9	7,9	1,6
13	35,1	3,6	9,7	1,9	2,0	5,1	2,4
14	35,3	3,4	9,7	2,4	2,2	5,5	2,6
15	35,4	2,4	10,7	2,3	2,4	5,9	2,9
16	35,6	1,8	10,6	2,0	2,1	5,5	2,5
17	35,8	1,0	4,8	3,3	2,3	8,7	2,3
18	36,1	1,6	8,3	2,2	2,1	5,7	2,1
19	36,4	2,2	10,8	2,0	2,2	5,5	2,7
20	36,9	1,9	7,2	2,9	2,3	7,9	2,5
21	37,1	2,2	10,5	2,1	2,3	5,8	2,8
22	37,2	3,3	10,8	2,3	(8,2)		3,2
23	38,1	1,7	8,4	2,5	(10,0)		3,8
24	38,1	2,2	9,0	2,5	2,7	7,2	3,7
25	38,3	3,5	11,4	2,7	2,5	6,1	3,0
26	38,4	3,0	10,3	2,4	(8,7)		3,7
27	38,6	2,7	10,9	2,7	(9,0)		4,1
28	38,7	2,8	8,5	2,8	(9,3)		2,5
29	39,5	3,7	12,4	2,1	(9,3)		3,1
30	39,5	3,5	11,8	2,3	(8,8)		3,5
31	39,6	4,4	8,0	4,2	2,4	5,9	3,0
32	40,0	3,5	11,2	2,7	(9,0)		4,0
33	40,4	3,1	10,0	2,4	(9,0)		4,6
34	40,5	3,2	11,4	2,8	(9,1)		4,1
35	40,6	3,1	11,6	2,9	(9,3)		4,0
36	41,3	3,0	12,0	2,9	(9,7)		4,2
37	41,7	3,9	13,6	3,2	3,0	7,6	3,5
38	42,0	4,7	10,8	3,3	(9,3)		3,8
39	43,2	4,7	7,7	4,5	(9,9)		4,1
40	43,8	3,2	9,4	2,0	(7,7)		2,5

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TABLE 2. INVESTIGATION RESULTS ON AROMATICS IN A REPRESENTATIVE SAMPLE OF HIGH-TEST GASOLINES SHIPPED TO WEST GERMAN GAS STATIONS 1971/72 [Oelert, 2]

No.	Weight %						
	Total aromatics	Benzene	Toluene	Ethylbenzene	p-xylene	m-xylene	O-xylene
1	32,4	2,5	7,0	1,7	(3,6)		2,2
2	38,5	2,5	8,3	1,9	(6,9)		2,7
3	43,5	5,4	5,4	4,3	2,2	5,7	3,2
4	43,7	4,1	12,2	4,3	(6,9)		1,9
5	44,7	2,9	11,9	2,0	(8,0)		2,9
6	45,3	3,3	14,6	3,3	1,0	3,9	1,0
7	45,6	7,0	15,8	2,2	(7,6)		2,8
8	46,2	1,4	13,6	2,8	2,6	6,1	3,4
9	46,9	2,4	12,6	2,9	3,2	8,7	3,8
10	47,1	6,3	12,7	2,7	(10,1)		3,9
11	47,1	5,6	11,6	2,5	(7,8		1,5
12	47,4	6,9	8,1	5,3	(10,0)		3,5
13	47,6	14,5	12,0	2,9	(6,2)		2,3
14	48,6	13,5	12,3	2,8	(6,2)		2,4
15	48,7	12,2	11,5	3,4	(7,4)		2,7
16	48,8	3,5	15,8	3,5	1,2	4,8	1,3
17	48,9	2,4	12,7	3,2	3,4	8,5	4,1
18	48,9	1,5	15,3	2,7	1,7	6,6	1,5
19	49,2	3,7	13,2	3,2	(12,3)		4,5
20	49,5	14,0	12,4	3,0	(6,4)		2,5
21	49,8	7,0	15,0	3,2	2,5	6,5	3,0
22	49,9	2,5	19,0	3,5	1,6	9,2	6,7
23	50,0	7,9	13,7	3,6	(9,2)		3,6
24	50,2	8,8	7,1	6,0	2,7	6,9	3,7
25	50,3	13,5	12,4	3,2	(7,2)		2,6
26	50,6	2,2	18,7	3,6	1,6	9,2	6,7
27	51,0	6,8	13,7	3,8	2,9	7,4	4,0
28	51,0	6,7	10,0	4,1	3,6	8,9	3,5
29	51,3	4,5	16,2	3,3	3,4	9,1	4,6
30	51,5	4,9	15,6	3,5	3,4	9,3	4,4
31	51,8	9,7	15,9	3,0	2,9	7,4	3,4
32	51,9	5,5	14,8	3,6	(11,0)		4,1
33	52,2	4,4	16,5	3,1	(12,7)		4,4
34	52,2	7,8	14,8	3,0	3,0	7,6	3,9
35	52,3	9,9	14,7	3,1	(9,5)		3,4
36	52,5	9,0	16,0	3,1	2,8	7,0	5,7
37	52,6	4,5	15,4	3,2	3,6	8,7	4,6
38	52,9	11,2	16,1	2,9	2,8	7,0	3,3
39	54,1	5,2	17,7	3,3	4,0	9,6	1,6
40	54,1	4,1	17,5	3,2	3,8	9,5	1,5
41	54,3	3,8	10,7	6,3	3,8	9,5	1,8
42	56,5	9,5	15,4	3,5	3,1	8,0	4,1
43	56,5	4,8	15,5	2,9	3,4	8,2	4,1
44	57,3	9,4	17,0	4,2	3,4	8,3	4,1

It is evident that values for total hydrocarbons (expressed as n-hexane) cannot be used to judge immision effects and cannot be used as the basis for threshold determinations of this unknown mixture. All that can be done at present — leaving techniques out of consideration — is to discuss the effects of hydrocarbons and groups of hydrocarbons emitted by vehicles; and to propose tentative thresholds.

Immission hydrocarbons can be grouped as follows:

1. paraffins,
2. naphthenes,
3. olefins and alkines,
4. aromatics,
5. oxidized hydrocarbons.

According to Oelert [2], these groups do not immediately derive from fuels; at least 60 - 70%, probably 70 - 80 mol/%, of hydrocarbons in exhaust must not be regarded as uncombusted hydrocarbons. In ordinary city traffic, exhaust composition is determined by the partially combusted fractions, not the noncombusted hydrocarbons.

The damaging effect of hydrocarbon immission is due to:

1. their inherent toxicity (e.g., toluene);
2. toxic metabolites produced in the body (e.g., benzene);
3. synergy with other pollutants (e.g., NO_2 and olefins);
4. involvement in "oxidant" formation (cf., Section 6.4).

Toxicologically and medically, it is undoubtedly the aromatics which are most important in hydrocarbon immission; next would be the highly reactive olefins and oxidized hydrocarbons; paraffins and naphthenes are of lesser significance.

7.2. Discussion of Individual Hydrocarbons and Groups of Hydrocarbons with Proposed Immission Limiting Value

7.2.1. Paraffins

Paraffins are saturated aliphatic hydrocarbons with low reactivity and toxicity. Molecules with 1 - 4 carbon atoms have the common names methane (CH_4), ethane (C_2H_6), propane (C_3H_8), and butane (C_4H_{10}); with higher C atoms (chains) they have Greek number names with the suffix "ane" (pentane C_5H_{12}, hexane C_6H_{14}, heptane C_7H_{16}, octane C_8H_{18}). All of these names also comprise all the isomers having the general formula C_nH_{2n+2} [Klages, 5]. They can be regarded as largely inert; inhalation of their vapor does not result in chemical bonding. Their intake and excretion follow purely physical laws, lipid affinity being decisive for absorption. As shown in Figure 1, absorption of this homologous series of paraffins increases in proportion to molecular size, which correlates with the narcotic effects of the individual paraffins [Wagner, 1]. Animal experiments by Fuehner [6], also confirm that the degree of narcotic effect rises with the molecular weight of the hydrocarbons tested (pentane, hexane, heptane, octane). Similar results were observed by Lazarew [7].

Since paraffins are not very dangerous and have nearly the same effects, we propose a common immission threshold.

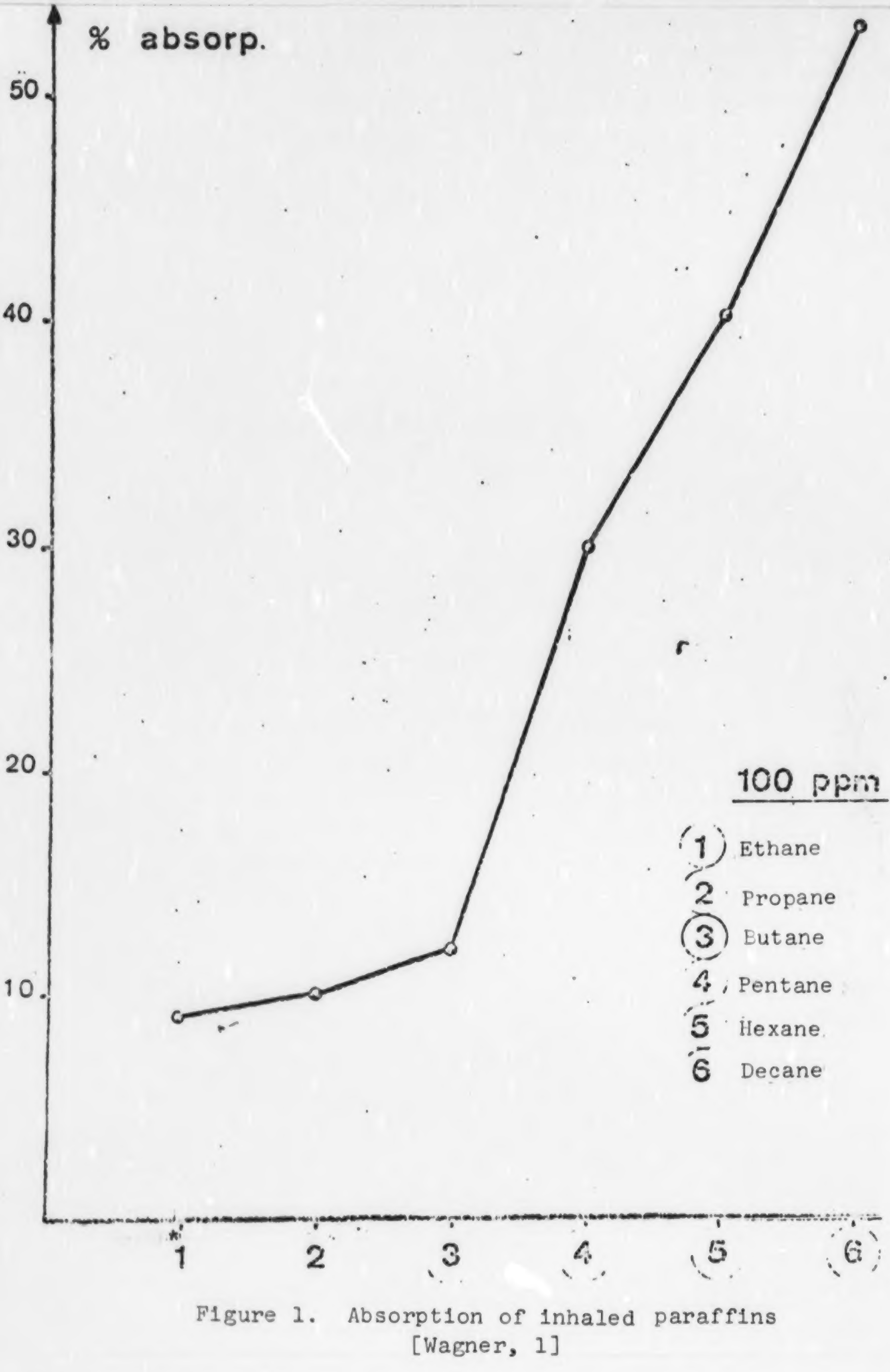

Figure 1. Absorption of inhaled paraffins [Wagner, 1]

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*Translator's Note: Illegible in foreign text.

	MIK_D (24 hrs)		MIK_K (30 min)	
	mg/m^3	ppm	mg/m^3	ppm
Methane	65,0	100,0	65,0	100,0
Ethane	65,0	53,0	65,0	53,0
Propane	65,0	36,0	65,0	36,0
Butane	65,0	27,5	65,0	27,5
Pentane	65,0	22,0	65,0	22,0
Hexane	65,0	18,5	65,0	18,5
Heptane	65,0	16,0	65,0	16,0
Octane	65,0	14,0	65,0	14,0
Nonane	65,0	12,5	65,0	12,5
Decane	65,0	12,0	65,0	12,0

7.2.2. Naphthenes

Napthenes are alicyclic compounds; basically they belong to the aliphatic hydrocarbons. If saturated, they are called cyclo-paraffins; if unsaturated, cyclo-olefins and cyclo-alkines. Benzene rings with 6 carbons, plus their derivatives and condensation products, are an exception because of their special chemical characteristics. Saturated naphthenes resemble paraffins. Best known among them are cyclo-paraffins, like cyclo-pentane, cyclo-hexane, etc., which have the general formula C_nH_{2n}. Correspondingly, the unsaturated olefinic compounds are called cyclo-pentene, cyclo-hexene, etc., and resemble the olefins. In effectiveness, they are ranged between the aliphatic and the aromatic hydrocarbons. Therefore, the maximum immission concentration values for cyclo-paraffins could be the same as for paraffins; and for cyclo-olefins — the same as for olefins.

7.2.3. Olefins and alkines

The structure of these hydrocarbons resembles that of the paraffins, but includes double (for olefins) and triple (for alkines) bonds. Olefins have the suffix "ylene" (ethylene, propylene, butylene, pentylene, etc.), and alkines — the suffix "ine". The names again include all the stereo-isomers having the general formula of C_nH_{2n} for olefins, and C_nH_{2n-2} for alkines.

These compounds have lower boiling points than the corresponding paraffins, and are much more reactive than the saturated hydrocarbons. Toxic effects show a rise with an increase in molecular weight. Because of their higher boiling points, however, the higher olefins play a lesser role as immission components. In setting possible thresholds, it must be remembered that the highly-reactive olefins and alkines might convert to other toxic compounds during emission, and play an essential part as catalysts for photochemical smog.

We propose the following common maximum immission concentration values for olefins and alkines:

$$3 \text{ mg/m}^3$$

for both MIK_D and MIK_K values.

7.2.4. Aromatic hydrocarbons

Toxicologically and medically, the most important group of hydrocarbons immitted are indubitably the aromatics. Considerable quantities are present in fuels: up to 45% in regular gasoline, and up to 60% in high-test gasoline (cf.,Tables 1 and 2). Large amounts of aromatics are also emitted by motor vehicles. According to Oelert [2], these are determined by fuel composition and engine condition. In spite of several attempts to correlate the amount of aromatics in automobile exhaust gases with that in fuel, no such estimate or factor can be derived from the fuel composition. Percentage contributions cannot as yet be attributed to any given engine type under various conditions. The amount of lower aromatics (for example, benzene) in fuel itself might be much lower than that in secondary sources. Benzene, among others, can also be formed by de-alkylization of higher aromatics. It is impossible to say to what extent the emitted aromatics should be regarded as uncombusted fuel components or as secondary products. Lower aromatics may still be assumed to be dependent on fuel composition. According to the most recent research, however, this has much less a bearing on the higher aromatics (e.g., carcinogenic polycyclic aromatics) than engine type, operation, and condition. The following table shows the relationship of aromatics emitted to various operating conditions; the data refer to one type of car and one fuel (consisting of 30% aromatics, 10% olefins, 60% paraffins) only.

	Neutral	Constant speed 50 kg/h	Acceleration 25-50 km/h	Deceleration 50-35 km/h
Benzene	35 ppm	17 ppm	20 ppm	185 ppm
Toluene	158 ppm	81 ppm	84 ppm	1,380 ppm
Xylene + ethyl benzene	50 ppm	25 ppm	26 ppm	371 ppm
Higher aromatics	78 ppm	34 ppm	36 ppm	375 ppm

For purposes of clarity, the aromatics are divided into benzene type and poly-cyclic aromatic hydrocarbons, each of which will be discussed separately because of their specific chemical and toxicological characteristics.

7.2.4.1. Benzene type aromatic hydrocarbons

A detailed discussion of the individual compounds in this group, many of which are very significant emission components, would be beyond the scope of this study; here we shall merely briefly sketch the impact of carcinogens and propose thresholds for the remainder. A detailed discussion of the effects of aromatics can be found in the monograph by Fodor* [8].

7.2.4.1.1. Benzene

Benzene is a colorless, highly volatile liquid with a characteristic odor. It is present in fuels to various degrees, up to 5% in regular gasoline, and up to 15% in high test gasoline. It is impossible to say how much of the benzene in automobile exhaust gases comes directly from fuel, and how much is due to secondary conversion. Under certain conditions, automobile exhaust emissions may contain 300 - 500 mg/m^3.

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*G. G. Fodor: Noxious Vapors. Dangers in Occupational and Every-Day Life from Aromatic Hydrocarbons. VDI-Verlag, 1972.

From the medical point of view, it is one of the most important vehicle emission components. Both the original entire molecule, as well as the poisonous metabolites formed by its breakdown in the body are dangerous. We therefore distinguish between nonspecific effects due to the benzene molecule itself (irritant and narcotic effect), and specific (e.g., hemotoxic) effects most probably due to metabolites.

Chronic benzene poisoning, with more or less destructive changes in organs responsible for blood production, can be the result of repeated intake of small quantities, unnoticeable either by smell or irritant qualities.

Exogenous and endogenous factors can influence the incidence of benzene intoxication.

Apart from length and degree of exposure, individual susceptibility to benzene plays a large part. This appears to be the only explanation for the many reports in which some of the subjects developed symptoms very soon, while others showed none for years, although external conditions seemed identical.

Latent infections or other impairment of the organism, on the other hand, also may cause or favor the onset of toxic symptoms. It must be pointed out that terminating the exposure does not stop the effects of benzene on the organism.

Not only can blood problems, once initiated, persist after exposure; there is also the possibility that symptoms can first appear months, years, even decades after the end of benzene exposure.

A renewed flare-up of benzene poisoning without any further exposures is also possible.

Malignant proliferations of the apparatus producing leucocytes, lymphocytes, and red blood cells are today viewed as most likely due to benzene intoxication.

Because of the potential danger of even the lowest benzene concentrations, no immission thresholds can be tolerated from a medical standpoint. A concentration of zero should be the object of all technical endeavors.

7.2.4.1.2. Homologs of benzene

Toluene, O-xylene, m-xylene, p-xylene, ethyl benzene, n-propyl benzene, i-propyl benzene 1,3,5,-trimethyl benzene, 1,2,4-trimethyl benzene, 1,2,3-trimethyl benzene, O-, m-, and p-ethyl toluene are all homologs of benzene significant in emissions and immissions. Isomers and similar substances are here treated collectively.

For toluene, we propose the following thresholds:

MIK-long-term value (MIK_D) of 1.8 mg/m^3 (0.50 ppm);
MIK-short-term value (MIK_K) of 5.4 mg/m^3 (1.40 ppm).

Xylene occurs as o-, m-, or p-xylene. All isomers are treated together here, and the following thresholds proposed:

MIK-long-term value (MIK_D) of 1.8 mg/m^3 (0.40 ppm);
MIK-short-term-value(MIK_K) of 5.4 mg/m^3 (1.20 ppm).

For ethyl benzene, we proposed the following thresholds:

MIK-long-term value (MIK_D) of 1.0 mg/m^3 (0.23 ppm);
MIK-short-term value (MIK_K) of 3.0 mg/m^3 (0.70 ppm).

N- and i-propyl benzene act similarly, and are here dealt with together under the name cumene. We propose the following thresholds:

MIK-long-term value (MIK_D) of 0.6 mg/m^3 (0.12 ppm);
MIK-short-term value (MIK_K) of 1.8 mg/m^3 (0.37 ppm).

Tri-methyl benzene exists in three isomers with the names: mesitylene, pseudo-cumene, and hemi-mellitone. We propose a common threshold of:

MIK-long-term value (MIK_D) of 0.3 mg/m^3 (0.06 ppm);
MIK-short-term value (MIK_K) of 0.9 mg/m^3 (0.18 ppm).

Ethyl toluene exists as o-, m-, and p-ethyl toluene. Their toxic effects might be similar to those of the xylenes and ethyl benzene. Toxic effects are largely unknown. We propose a common threshold of:

MIK-long-term value (MIK_D) of 1.0 mg/m^3 (0.20 ppm);
MIK-short-term value (MIK_K) of 3.0 mg/m^3 (0.60 ppm).

7.2.4.1.3. Polynuclear hydrocarbons

Gas-chromatographic studies have shown that numerous poly-aromatics are present in automobile exhaust gas condensate; only some of them have been identified. Table 3 represents the polynuclear hydrocarbons isolated by Hoffman and Wynder [9, 10].

TABLE 3. POLYNUCLEAR AROMATIC HYDROCARBONS ISOLATED FROM GASOLINE ENGINE EXHAUST "TAR" (from Hoffman and Wynder, [10])

Hydrocarbon	Carcinogenic Activity[a]	Fraction	Amount Isolated[b,c]		
			ug	Ppm	ug/1-min run
Benzo(a)pyrene	+++	14	158,1	31,5 (72,6 ± 3,6)	2,2 (5,0)
Dibenz(a,h)anthracene	+++	18	11,6	2,5	0,16
Benzo(j)fluoranthene	++	14, 16	86,6	17	1,2
Benzo(b)fluoranthene	++	13, 14	332	64	4,4
Benz(a)anthracene	+	10, 11	310	61,7 (131,4 ± 6,5)	4,2 (9,0)
Benzo(e)pyrene	+	13, 14	2 120	422	29,0
Indenol(1,2,3-cd)pyrene	+	17	414	82	5,7
Chrysene	+	13, 14	880	175	12,0
Alkylbenzo(a)pyrene	?	14	50	1	0,07
Alkylbenz(a)anthracene	?	12	10	2	0,14
Alkylchrysene	?	13, 14, 15	334	67	4,6
Indeno (1,2,3-cd)fluoranthene	?	17	13	3	0,18
Benzo(ghi)perylene	–	12, 13, 14	25	51	3,5
Perylene	–	11	Trace	Trace	Trace
Triphenylene	–	12	220	44	3,0
Pyrene	–	3, 4, 5	8 880	1 770	122,0
Alkylpyrene	?	13	40	8	0,06
Fluoranthene	–	5, 6	4 880	972	60,0
Alkylfluoranthene	?	6 - 11	1 312	261	17,9
Anthanthrene	–	15	223	44	3,1
Benzo(k)fluoranthene	–	16, 17	270	54	3,7
Benzo(ghi)fluoranthene	–	7, 8, 9	750	150	10,2
11 H-benzo(b)fluorene	–	6, 11	254	51	3,5
Coronene	–	15, 16	1 692	338	23,2

[a] Relative carcinogenic activity on mouse skin: +++, active; ++, moderate; +, weak; ? , unknown; –, inactive.

[b] Values based on material from the first run of the gasoline engine.

[c] Figures in parentheses indicate actual amounts present in the extract, calculated by tracer technique.

7.2.4.1.3.1. Concentrations of polyaromatics

In evaluating data on concentrations of polyaromatics in automobile exhaust gases or the atmosphere, the chief difficulty is the difference in the methods used for the measurements reported in the literature over the past 15 years. Not only can Otto engines differ greatly from each other in their output of polyaromatics: the automobile exhaust gas from one and the same vehicle depends very much on the age of the engine, its tuning, temperature, load, etc. Automobile exhaust gas collection methods and chemical analysis methods also affect the results. There is a great need for standardizing the conditions (e.g., the Europa-cycle) under which measurements on modern engine types are carried out.

It is therefore not too meaningful to go into detail on old results obtained under the most widely varying conditions. We shall confine ourselves to concentrations of one representative of the polyaromatics in the atmosphere, which has been investigated more than all the others: benzo(a)pyrene (BaP).

7.2.4.1.3.2. Concentrations of BaP in the atmosphere

The comments on polyaromatics also pertain to the quantitative BaP analysis: many different methods have been used in the past decade, and have led to different results. The present values are, therefore, hard to equate. This is demonstrated by a study of Bravo et al. [14], in which a Canadian — as opposed to a U.S.A. — method for BaP analysis of aerosols in Mexico City registered 10 - 15 times the amount of BaP.

BaP values for various regions can, therefore, be compared only if they were obtained by the same researcher. However, in comparing data of different workers on metropolitan BaP concentrations, it is remarkable that considerably less BaP is found in the U.S.A. than in the air of large European cities. Colucci and Begemann [12] have summarized data from the world literature as follows:

TABLE 4. BENZO(a)PYRENE CONTENT OF URBAN AIR (from Colucci and Begemann [12])

Investigators	City	Benzo(a)pyrene, µg/10³m³			
		Spring	Summer	Fall	Winter
Colucci and Begeman, this report	New York:				
	Commercial	0,5 - 8,1	0,7 - 3,9	1,5 - 6,0	0,5 - 9,4
	Freeway	0,1 - 0,8	0,1 - 0,7	3,3 - 3,5	0,7 - 1,3
	Residential	0,1 - 0,6	0,1 - 0,3	0,6 - 0,8	0,5 - 0,7
Colucci and Begeman, 1965	Detroit:				
	Central sites Commercial	7,2	. . .	. . .	5,0 - 17,0
	Freeway	. . .	4,0 - 6,0	3,4 - 7,3	9,2 - 13,7
	Residential	. . .	0,2	. . .	0,9 - 1,8
Sawicki et al., 1960	Atlanta	2,1 - 3,6	1,6 - 4,0	12 - 15	2,1 - 9,9
	Birmingham	6,3 -18	6,1 -10	20 - 74	23 - 34
	Cincinnati	2,0 - 2,1	1,3 - 3,9	14 - 18	18 - 26
	Detroit	3,4 -12	4,1 - 6,0	18 - 20	16 - 31
	Los Angeles	0,4 - 0,8	0,4 - 1,2	1,2 - 13	1,6 - 6,6
	Nashville	2,1 - 9,0	1,4 - 6,6	30 - 55	25
	New Orleans	2,6 - 5,6	2,0 - 4,1	3,6 - 3,9	2,6 - 6,0
	Philadelphia	2,5 - 3,4	3,5 -19	7,1 -12	6,4 - 8,8
	San Francisco	0,8 - 0,9	0,2 - 1,1	3,0 - 7,5	1,3 - 2,4
DeMario and Corn, 1966	Pittsburg	. . .	0 - 23	2,9 -37	8,2
Hettche, 1964	Hamburg, Germany	14 - 72	10 - 26	66 - 296	94 - 388
Waller, 1952	London, England	25 - 48	12 - 21	44 - 122	95 - 147
	Sheffield, England	20 - 44	21 - 33	56 - 63	64 - 78
	Cannock, England	4 - 16	6 - 11	27 - 31	27 - 32
Waller et al., 1965	London (in traffic)	20	11	57	68
	London (background)	11	1	38	42
D'Ambrosio et al., 1958	Milan, Italy	12	3	25	150
Campbell and Clemmesen, 1956	Copenhagen, Denmark	6	5	14	15
Skramovsky, 1963	Prague, Czechloslovakia	. . .	13 - 36	. . .	53 - 145
Saringer, 1963	Budapest, Hungary	. . .	17 - 32	. . .	72 - 141
Louw, 1965	Pretoria, South Africa	. . .	10	. . .	22 - 28
	Johannesburg, South Africa	. . .	. . .	. . .	22 - 49
	Durban, South Africa	. . .	. . .	. . .	5 - 28
Watanabe and Tomita, 1966	Osaka, Japan				
	Commercial	5,7	2,7	9,4	14
	Residential	3,3	1,4	3,8	6,7
Cleary and Sullivan, 1965	Sidney, Australia	0,6 - 2,4	0,6 - 1,8	2,5 -7,4	3,8 - 8,2

In addition, we should like to report the results obtained by Friedrichs et al. [13], who measured BaP concentrations a at 13 test sites in the Ruhr valley in 1968. Annual averages for the stations ranged from 30 - 250 ng BaP/m^3; the total average for all 13 stations can be calculated to be 112 ng/m^3.

The BaP concentrations in Table 4 show distinct differences between summer and winter. The lower figures for summer are in part due to a greater UV-intensity, which destroys BaP; to a lesser extent they also reflect the lower contributions of heating plants during the warm season.

7.2.4.1.3.3. Sources of BaP in the atmosphere

BaP is formed during incomplete combustion. According to present data, it is heating plants which produce by far the greater portion of BaP emission; vehicles contribute only a small amount. Estimates for BaP emission in the U.S. run to 481 t as the total for the year; 418.3 t were attributed to heating plants, and only 20.6 t to cars [Olsen and Haynes, 14]. On the basis of his measurements in the U.S., Begeman [15] estimates that in suburbs, only 1.8% of the BaP content of the air is due to traffic.

A study edited by the Ministry for Work, Health, and Welfare in NRW (State of **North Rhine-Westfalia [3] states that** during combustion of 1 liter of gasoline, an internal combustion engine emits 72 μg BaP, and 400 mg lead, i.e., a ratio of BaP : lead of 1 : 5,500. In city traffic, however, only a small part of the 0.4 g/l of lead added to gasoline is emitted into the air. Even if we assume a 1 : 500 ratio of BaP : lead in automobile exhaust gases, the concentrations of these two substances in the open air - especially in winter — will be much closer. We might start with a BaP content of 0.1 $\mu g/m^3$ and a lead content of 2 $\mu g/m^3$ air: this is a ratio of 1 : 20.

7.2.4.1.3.4. Effects of benzo(a)pyrene and other polycyclic hydrocarbons

In animal experiments, benzo(a)pyrene has a strongly carcinogenic effect, which was first described in 1915 by the Japanese Yamagiwa and Ichikawa (quoted in Shimkin [16]). In 1930, Kennaway et al. (quoted in Shimkin [16]) first isolated it from anthracene tars; since then, it has been regarded as the chief cause for the carcinogenic effects of tar and soot. As early as 1775, Pott (quoted in Falk et al.,[17]) associated the frequency of scrotal cancers in chimney sweeps with the effects of soot. Later, similar correlations were established in many cases for workers in certain professions.

Data from occupational medicine on the effects of very high concentrations of toxic materials offer no conclusions as to whether, and to what extent, the atmospheric content of benzo(a)pyrene or other carcinogens has contributed to the rise in lung cancer frequency within the last decades. There are no data on the dosages of carcinogens inhaled during the years in question, nor even on individual cases which might throw some light on dosage-to-effect relationships. In animal experimentation, we have many studies on the carcinogenic effects of several polynuclear hydrocarbons, expecially of benzene(a)pyrene (cf.,Table 3). But these are results of experimental models which permit no conclusions about the effect of this material on man under ordinary living conditions.

Several authors have performed experiments on animals with extracts from air-borne dusts in metropolitan areas, with automobile exhaust gas tars and with cigarette tars [Hoffman and Wynder, 10; Dontenwill et al., 18; Falk et al., 17a, b; Hoffman et al., 19; Wynder and Hoffman, 24; Rigdon and Neal, 20; Hueper et al., 21]. Summarizing the results of all these tests seems to indicate that the carcinogenic effect of a complex mixture does not parallel the BaP content, since other materials can raise as well as lower the rate of tumor formation. This obscures the dosage-vs.-effect relationships even more. The probably low contribution of automobile exhaust gases to the BaP content in metropolitan atmospheres does not signify a correspondingly lower carcinogenic stress for man by this emission.

Hettche's interpretation of his recent epidemiological investigations [22], pointing out the predominant influence of automobile exhaust gases on lung cancer in man, is not convincing on the basis of the above material. It has already been critically reviewed by Schmidt [23].

Until now, we are lacking basic knowledge to formulate adequate scientific conclusions on: which concentrations of polyaromatics in the air, individually or jointly, are medically harmless for life spans of 80 - 100 years? and, what are the dosages and latency periods after which we can count on a certain rise in the lung cancer rate? Since these are very difficult and complex questions, it will be years before we will achieve a scientific basis for any decisions.

7.2.5. Oxidated hydrocarbons

Oxidated hydrocarbons constitute only about 5% of the total organic compounds emitted; however, since they are highly irritating to the mucosa and the sense of smell, they can put a considerable burden on the population (cf. also Section 6.4, Oxidants). Among them are the aldehydes, ketones, alcohols, acetales, furanes and phenols.

We propose the following thresholds for some of the more important oxidated hydrocarbons:

Acrolein:

MIK-long-term value (MIK_D) of **0,003 mg/m^3** (0,001 ppm).
MIK-short-term value (MIK_K) of **0,010 mg/m^3** (0,004 ppm)

Formaldehyde:

MIK-long-term value (MIK_D) of **0,020 mg/m^3** (0,020 ppm)
MIK-short-term value (MIK_K) of **0,050 mg/m^3** (0,040 ppm)

Ethylene oxide:

MIK-long-term value (MIK_D) of 0,100 mg/m^3 (0,060 ppm)
MIK-short-term-value (MIK_K) of 0,500 mg/m^3 (0,300 ppm)

Phenol:

MIK-long-term value (MIK_D) of 0,200 mg/m^3 (0,050 ppm)
MIK-short-term value (MIK_K) of 0,400 mg/m^3 (0,100 ppm)

Cresols:

MIK-long-term value (MIK_D) of 0,200 mg/m^3 (0,040 ppm)
MIK-short-term value (MIK_K) of 0,400 mg/m^3 (0,080 ppm)

Acetaldehyde:

MIK-long-term value (MIK_D) of 4,0 mg/m^3 (2,2 ppm)
MIK-short-term value (MIK_K) of 10,0 mg/m^3 (6,6 ppm)

Acetone:

MIK-long-term value (MIK_D) of 10,0 mg/m^3 (4,2 ppm)
MIK-short-term value (MIK_K) of 30,0 mg/m^3 (13,0 ppm)

REFERENCES

(Section 7, Hydrocarbons)

1. Wagner, H. M. Absorption of Several Hydrocarbons During Inhalation. Congress Volume of the Hungarian Association for Industrial Medicine, Budapest, 1971.

2. Oelert. H. H. An Approach to Special Problems in Measuring Individual Immitted Hydrocarbons. Unpublish report.

3. Materialien zum Umweltprogramm der Bundesregierung, 1971 (Papers on the Environmental Program of the Federal Government. Published by the Federal Minister of Interior. Separate Appendix to 6th Federal German Election Papers VI/2710.

4. Reine Luft für Morgen. Utopie oder Wirklichkeit? Ein Konzept f. d. Land NRW,bis 1980 (Clean Air for Tomorrow. Utopia or Reality? A Concept for the State of North Rhine-Westphalia up to 1980). Published by the Minister of Labor, Health, and Social Welfare to the State of North Rhine-Westphalia. Dortmund, Westphalia, 1972.

5. Klages, F. Hydrocarbons. In: The Fischer Lexicon of Chemistry. Frankfurt, Fischer Verlag, 1971.

6. Führer. Biochem. Ztschr., Vol. 115, 1921, p. 235. Cited by Flury, F. and F. Zernik. Schädliche Gase, Dampfe, Nebel, Rauch- und Staubarten (Noxious Gases, Vapors, Fogs, Smokes and Dusts). Berlin, Verlag J. v. Springer, 1931.

7. Lazarew, N. W. On the Toxicity of Various Hydrocarbon Fumes. Arch. epx. Pathol. Pharmak., Vol. 143, 1929, p. 223.

8. Fodor, B. B. Schädliche Dampfe. Die Gefährdung des Berufs- und Alltagslebens durch Kohlenwasserstoffe (Noxious Vapors. Dangers in Occupational and Every-day Life from Aromatic Hydrocarbons). VDI-Verlag, 1972.

9. Hoffmann, D. and E. L. Wynder. Analytical and Biological Studies on Gasoline Engine Exhaust. Natl. Cancer Inst. Monogr., Vol. 9, 1962, pp. 91-116.

10. Hoffmann, D. and E. L. Wynder. Studies on Gasoline Engine Exhaust. J. Air Poll. Control Assn., Vol. 13, 1963, pp. 322-327.

11. Bravo, H. et al. Concentrations of Lead, BaP, and BkF in the Atmosphere of Three Mexican Cities. In: Proceedings of the Second International Clean Air Congress. Editors, H. M. Englund and W. T. Beery. New York, London, Academic Press, 1971, pp. 118-121.

12. Colucci, J. M. and Ch. R. Begeman. Carcinogenic Air Pollutants in Relation to Automotive Traffic in New York. Environmental Science and Technol., Vol. 5, 1971, pp. 145-150.

13. Friedrichs, K.-H., J. Stuke, A. Brockhaus and H. Steiger. Air Pollution in the Ruhr — Evaluation of a Test Program From an Environmental Viewpoint. Staub-Reinhaltung der Luft, Vol. 31, 1971, pp. 323-326.

14. Olsen, D. and J. L. Haynes. Preliminary Air Pollution Survey of Organic Carcinogens. U. S. Dept. of Health, Education and Welfare. Raleigh, N.C., 1969, 117 pp.

— Natl. Air Pollution Control Administration Publ. No. APTD 69-43.

15. Begeman, Ch. R. Carcinogenic Aromatic Hydrocarbons in Automobile Effluents. In: Vehicle Emissions. New York, Soc. of Automotive Engineers, 1964, pp. 163-174.

— Technical Progress Series, 6.

16. Shimkin, M. B. Environmental Carcinogens. Arch. Environ. Health, Vol. 16, 1968, pp. 513-521.

17a. Falk, H. L., P. Kotin and A. Mehler. Polycyclic Hydrocarbons as Carcinogens for Man. Arch. Environ. Health, Vol. 8, 1964, pp. 721-730.

17b. Falk, H. L., P. Kotin, and S. Thompson. Inhibition of Carcinogenesis. Arch. Environ. Health, Vol. 9, 1964, pp. 169-179.

18. Dontenwill, W., H. Elmenhorst, H.-P. Harke, G. Reckzeh, K. H. Weber in collaboration with J. Misfeld and J. Timm. Experimental Determinations of the Carcinogenic Effects of Cigarette Tars on the Skin of Mice. Part 1: Collaboration. Z. Krebsforsch., Vol. 73, 1970, pp. 265-284.

19. Hoffmann, D., E. Theisz and E. L. Wynder. Studies on the Carcinogenicity of Gasoline Exhaust. J. Air Poll. Control Assn., Vol. 15, 1965, pp. 162-165.

20. Rigdon, R. H. and O. Neal: Tumors in Mice Induced by Air Particulate Matter from a Petrochemical Industrial Area. Texas Rep. Biol. Med., Vol. 29, 1971, pp. 109-123.

21. Hueper, C., P. Kotin, E. C. Tabor, W. W. Payne, H. Falk and E. Sawicki. Carcinogenic Bioassays on Air Pollutants. Arch. Pathol., Vol. 74, 1962, pp. 89-116.

22. Hettche, H. O. Air Pollution and Lung Cancer. Naturwissenschaften, Vol. 58, 1971, pp. 409-413.

23. Schmidt, F. Cause of Cancer: Exhaust Gas or Tobacco Smoke? Umwelt, Vol. 6, 1971, pp. 28-30.

24. Wynder, E. L. and D. Hoffmann. Some Laboratory and Epidemiological Aspects of Air Pollution Carcinogenesis. J. Air Poll. Control Assn., Vol. 15, 1965, pp. 155-159.